Prediction of clinical bacteriological efficacy of oral antibiotics using a mechanism-based pharmacokinetic-pharmacodynamics modeling

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The objective of this study was to predict the clinical bacteriological efficacy of antibiotics and to examine the pharmacodynamics（PD）characteristics of antibiotics against bacterial strains using a mechanism-based pharmacokinetic-pharmacodynamics（PK-PD）modeling developed on the basis of interaction between drug concentrations and antibacterial activities.

Dynamic PD parameters（ε, γ, EC_{50}）and growth rate of organisms（λ）were obtained from *in vitro* time-kill profile data of oral antibiotics, tebipenem pivoxil（TBPM-PI）and cefditoren pivoxil（CDTR-PI）against *Streptococcus pneumoniae* or *Haemophilus influenzae.* PD characteristics of both drugs against *S. pneumoniae* or *H. influenzae* were examined, which indicated TBPM was concentration-dependent as well as time-dependent, and CDTR was mainly time-dependent to exhibit their bactericidal activities. Next, we simulated TBPM and CDTR concentrations in plasma after oral administration according to the dosage regimen of each drug specified in package insert, using population pharmacokinetic parameters of both drugs in pediatric patients with infections. In addition, changes in viable *in vivo* bacterial counts in humans were simulated using dynamic PD parameters and mean plasma concentrations of each drug. As a result, simulated profile of viable counts of *S. pneumoniae* and *H. influenzae* were well corresponding to the bacteriological efficacy results in clinical double-blinded comparative study of TBPM-PI and CDTR-PI in oral administration to pediatric patients with acute otitis media.

As mentioned in the above, it was considered to be possible to clarify the PD characteristics of TBPM and CDTR against each bacterial strain using the mechanism-based PK-PD model developed on the basis of interaction between drug concentrations and antibacterial activities, and to estimate the clinical bacteriological efficacy of those drugs.

Introduction

Pharmacokinetic-pharmacodynamics（PK-PD）approach plays an important role in establishing optimum dosing conditions for antibiotics and designing individualized dosage regimen.

Among PK-PD approaches of antibiotics, there is static MIC approach[1] developed by using MIC data and it is commonly used for research and development of antibiotics and appropriate usage of those. In the static MIC approach, C_{max}/MIC, AUC/MIC, and time above MIC were used as PK-PD parameters. It has a concept that PK-PD parameters that are correlated to the efficacy of an antibiotic differ depending on PD characteristics of the antibiotic, and there are target values for PK-PD parameters at which the antibiotic may exert its efficacy. A lot of reports have pointed out that static MIC approach would produce good correlations between the target values and clinical efficacy as a merit[2~4]. On the other hand, static MIC approach has the following three problems: 1）A large scale of animal experiments is required to determine PD characteristics, which may raise a controversial issue in terms of animal welfare. 2）It is not possible to see the interaction between the concentrations and bactericidal effects at the concentrations exceeding the MIC. 3）It is not possible to explain sub-MIC effect[5].

Sato, *et al.* broke through the above-mentioned problems and reported the following concept as mechanism-based PK-PD approach[6]. That is to say, “Direct interaction between antibiotics and bacterial strains is characterized by dynamic PD parameters（ε, γ, EC_{50}）and the growth rate of a microorganism（λ）, and the time course of *in vivo* antibacterial efficacy is almost determined by these PD parameters and the *in vivo* drug concentration profile. In the process for mechanism-based PK-PD approach, *in vitro* time-kill profile data is analyzed by the model, and PD parameters that quantify the interaction between bactericidal effects and antibiotic concentrations are obtained. In addition, if PK information（plasma concentrations, *etc*.）has been combined with PD parameters, it is possible to carry out *in vivo* PD estimation. Sato, *et al.* set up the following criteria to speculate PD characteristics from dynamic PD parameters.

1） if the ε/λ is about 10 or greater, and γ is about 1 or less, the pharmacodynamics should be “concentration-dependent”.
2） if the ε/λ is within the range of 1 to 2, and γ is about 5 or more, the pharmacodynamics should be “time-dependent”.
3） if the ε/λ is within the range of 1 to 4, and γ is within the range of 1 to 12, the pharmacodynamics should be “time-dependent” or “both concentration- and time-dependent”.

The PD characterization of antibiotics against various strains of different microorganisms can be predicted relatively easily by utilizing these criteria. They reported that these findings would make it possible to determine the kinds of causative pathogens to which the antibiotics should be applicable, and to establish the optimum dosage regimens in clinical sites.

However, possibility of clinical application has not been discussed yet in a previous report[6],

although the PD characteristics of various antibiotics were analyzed.

In this study, we therefore examined whether mechanism-based PK-PD approach would be able to predict *in vivo* bacteriological effects using oral carbapenem antibiotic, tebipenem pivoxil（TBPM-PI, orapenem®, an active substance; TBPM, Meiji Seika Pharma Co., Ltd.）and oral cephem antibiotic, cefditoren pivoxil（CDTR-PI, MEIACT®, an active substance; CDTR, Meiji Seika Pharma Co., Ltd.）. The dosage regimen of CDTR-PI to pediatric patients is to be oral administration at one time dose of 3 mg/kg after meal, 3 times daily. The maximum dose of 6 mg/kg, 3 times daily is applicable for treatment of pediatric bacterial pneumonia, acute otitis media, and acute rhinosinusitis, to which drug-resistant bacteria are largely involved.

We used *Streptococcus pneumoniae* and *Haemophilus influenzae* that have been frequently isolated as causative pathogens for major indications of above-mentioned two drugs（pediatric respiratory infections）. The profile of *in vivo* bacterial counts, which was estimated by dynamic PD parameters of each drug and population pharmacokinetic parameters in children, was compared with clinical trial results to discuss mechanism-based PK-PD approach. In addition, the PD characteristics of both antibiotics were examined against *S. pneumoniae* and *H. influenzae* as follows.

Materials and Methods

Microorganisms

Clinical isolates, *S. pneumoniae*; TH-1230, MSC-33（PRSP）and *H. influenzae*; MSC-238（BLNAS）, HI00542（BLNAR）were used in this study. Already determined and published values by broth microdilution method were used as MIC against each bacterial strain[6,7]（Table 1）. As for dynamic PD parameters of TBPM and CDTR against *S. pneumoniae*; TH-1230, MSC-33（PRSP）and *H. influenzae*; MSC-238（BLNAS）, already published data[6] were used（Table 1）.

Table 1. MICs and dynamic PD parameters* of antibiotics against strains of *S. pneumoniae* and *H. influenzae*

Antibiotics	Bacteria		Strains	MIC μg/mL	λ hr^{-1}	ε hr^{-1}	γ	EC_{50} μg/mL	ε/λ	SC μg/mL
TBPM	*S.pneumoniae*	PRSP	TH-1230	0.063	1.20	3.62	3.27	0.046	3.0	0.037
	S.pneumoniae	PRSP	MSC-33	0.063	1.31	3.31	2.13	0.039	2.5	0.032
	H.influenzae	BLNAS	MSC-238	0.125	0.83	2.15	1.54	0.037	2.6	0.027
	H.influenzae	BLNAR	HI00542	0.5	1.17	6.00	0.29	10.000	5.1	0.075
CDTR	*S.pneumoniae*	PRSP	TH-1230	1	1.15	2.63	10.40	0.94	2.3	0.920
	S.pneumoniae	PRSP	MSC-33	1	1.28	2.82	2.31	0.56	2.2	0.520
	H.influenzae	BLNAS	MSC-238	0.063	0.83	2.16	2.21	0.018	2.6	0.015
	H.influenzae	BLNAR	HI00542	0.5	0.92	5.18	0.20	10.703	5.6	0.005

*; TH-1230, MSC-33, MSC-238: reference 6）, HI00542: reference 7）

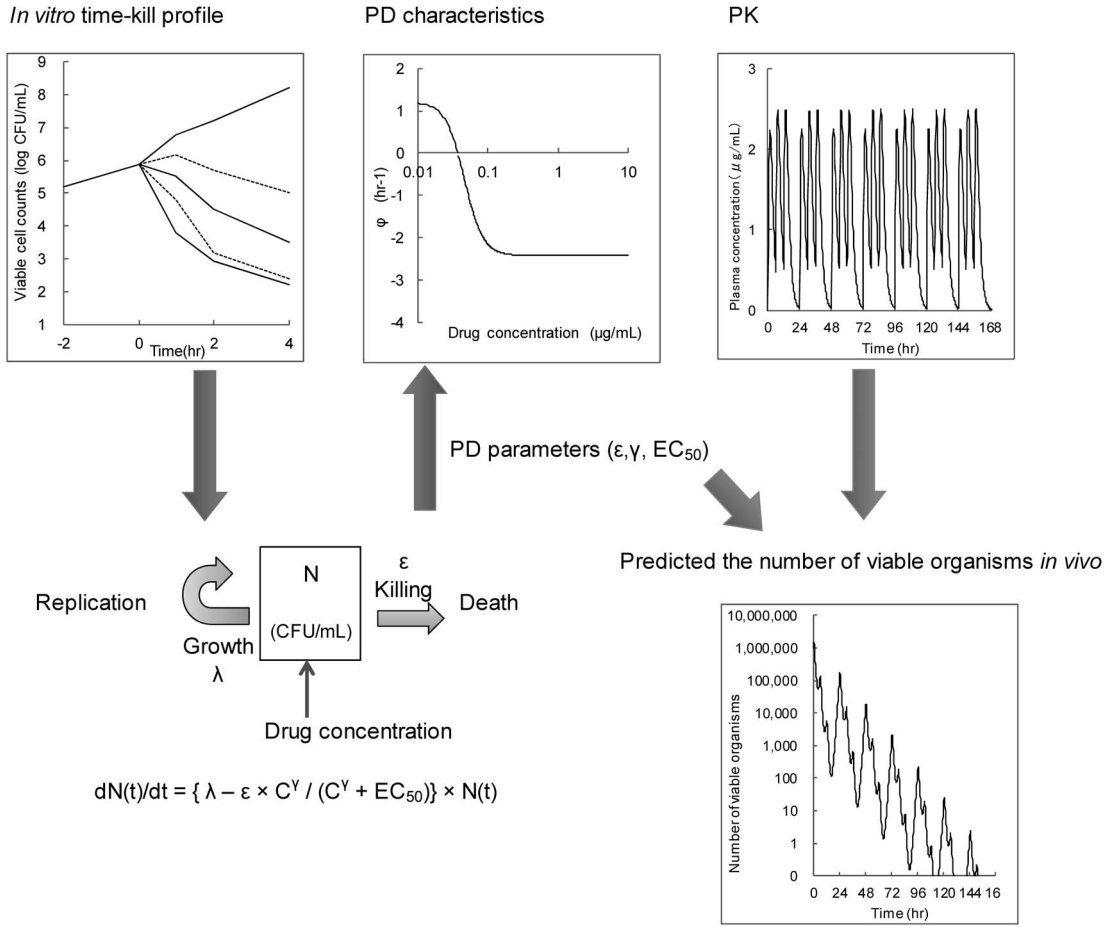
Dynamic PD parameters of TBPM and CDTR against *H. influenzae*；HI00542（BLNAR）were calculated as described in the "PK-PD Model" section on the basis of already reported[7] *in vitro* time-kill profile data.

PK-PD model

Fig. 1 explains the concept of mechanism-based PK-PD approach based on the interaction between drug concentrations and antibacterial effects. The following formula（modified E_{max} model）was used for analyzing time-kill profile and simulating *in vivo* bacterial counts[6,8,9].

$$dN(t)/dt = \{\lambda - \varepsilon \times C^{\gamma}/(C^{\gamma} + EC_{50})\} \times N(t) \qquad \text{Eq 1}$$

Fig. 1. Schematic illustration of the general concept of the mechanism-based PK-PD approach



t（hr）: the time after addition of antibiotics
N（t）（CFU/mL）: the number of viable organisms at time t
C（μg/mL）: the concentration of antibiotics
λ（hr^{-1}）: Growth rate constant of the organisms without exposure to antibiotics
ε（hr^{-1}）: the maximum kill rate constant
γ; Hill coefficient
EC_{50}（μg/mL）: the concentration of antibiotics at which 50% of the maximum effect is obtained

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λ（hr^{-1}）: Growth rate constant of the organisms without exposure to antibiotics

ε（hr^{-1}）: the maximum kill rate constant

γ: Hill coefficient

EC_{50}（μg/mL）: the concentration of antibiotics at which 50% of the maximum effect is obtained.

PD parameters that specify the interaction between antibiotics and bacterial strains are ε, γ, EC_{50}.

In addition, Eq1 was integrated by time（t）to have Eq2 for simulating time-course changes in bacterial counts（N）.

$$N(t) = N(0) \times \exp[\{\lambda - \varepsilon \times C^{\gamma}/(C^{\gamma} + EC_{50})\} \times t] \quad \text{Eq 2}$$

The term $\{\lambda - \varepsilon \times C^{\gamma}/(C^{\gamma} + EC_{50})\}$ on the right-hand side of Eq1 describes the net antibacterial activity（φ）of an antibiotic as a difference between the growth rate of organism and the kill rate of the antibiotic. The antibacterial activity is defined as function of antibiotic concentrations in the following formula.

$$\varphi = \lambda - \varepsilon \times C^{\gamma}/(C^{\gamma} + EC_{50}) \quad \text{Eq 3}$$

A positive value of φ indicates bacterial growth, and a negative value indicates a decrease in bacterial counts. The smaller the φ is, the stronger the bactericidal efficacy is. The φ value when the bactericidal efficacy has reached maximum was defined as φ_{max}. The interaction between the drug concentration and φ was displayed in a curve to examine the PD characteristics of antibiotics. The φ_{max} is obtained when C value has set to be infinity in Eq3, and described by Eq4.

$$\varphi_{max} = -(\varepsilon - \lambda) \quad \text{Eq 4}$$

In order to specifically understand the relationship between φ_{max} and the rate of decrease in the number of organisms, the time required to attain a 1 log reduction of the number of organisms（$t_{1/10}$）was obtained by assuming $N(t) = N(0)/10$ in Eq2（Eq5）.

$$t_{1/10} = -2.303/\varphi_{max} \quad \text{Eq 5}$$

Stationary concentration（SC）is defined as a drug concentration at which the growth rate equals the kill rate[8], as shown in the following formula. SC indicates the drug concentration where there is no net change in the number of organisms in a time-course manner, that is, static condition（$dN/dt = 0$）. The SC is obtained by introducing $dN/dt = 0$ into Eq1, as shown in the following formula.

$$SC = \{\lambda/(\varepsilon - \lambda)\}^{1/\gamma} \times EC_{50} \quad \text{Eq 6}$$

The time-kill profile data of TBPM and CDTR against *S. pneumoniae* or *H. influenzae* were analyzed by Eq1 to obtain the growth rate（λ）, ε, γ and EC_{50}. The SC was calculated by Eq6. In addition, *in vivo* bacterial counts were simulated on the basis of those PD parameters and clinical plasma concentrations of the drug. The number of viable microorganisms at the time of administration was fixed to be 1×10^6（CFU/mL）. Phoenix WinNonlin（ver.6.1, Pharsight Corporation）was used for PK and PK-PD analyses.

Population pharmacokinetic parameters

Population mean pharmacokinetic parameters proposed by Sato, *et al.* were used for simulating plasma concentrations of TBPM in pediatric patients[10]. The population pharmacokinetic analysis was conducted using plasma concentrations of samples obtained from Japanese pediatric patients（217 subjects, 395 sampling points; dosage at 4～6 mg/kg）（Table 2）. Means of demographic data of the patients were used as covariates that affected population mean parameters. Population mean pharmacokinetic parameters proposed by Matsumoto, *et al.* were used for simulating plasma concentrations of CDTR in pediatric patients[11]. The population pharmacokinetic analysis was conducted on plasma concentrations of samples obtained from Japanese and American pediatric patients（153 subjects, 578 sampling points; dosage of 5.62±1.62 mg/kg）（Table 2）. Means of demographic data of the patients were used as covariates that affected population mean parameters.

Clinical trial

Phase III study results in pediatric patients with acute otitis media[12] were used as control for comparison of *in vivo* bacterial counts estimated by mechanism-based PK-PD analysis（Table 3）. This Phase III study was performed as double-blinded comparative study with the high dose of CDTR-PI as control to examine the efficacy and safety of TBPM-PI in treatment of pediatric acute otitis media. TBPM-PI was orally administered at one time dose of 4 mg/kg（3.5 mg/kg or

Table 2. Population mean pharmacokinetic parameters in pediatric patients

TBPM-PI		
ka（hr^{-1}）	=	5.85
CL/F (L/hr/kg)	=	0.75
Vd/F（L/kg）	=	0.963
Tlag (hr)	=	0.239
CDTR-PI		
ka（hr^{-1}）	=	0.527
CL/F (L/hr/kg)	=	0.64
Vd/F（L/kg）		0.77
Tlag (hr)	=	0.282

Table 3. Bacteriological efficacy（eradication）after 3 days and 7 days administration

Pathogen in patients	TBPM-PI		CDTR-PI	
	Day 3	Day 7[1)]	Day 3	Day 7[1)]
S.pneumoniae	100.0 (27/27)	100.0 (31/31)	63.6 (21/33)	96.8 (30/31)
H.influenzae	96.0 (24/25)	100.0 (69/69)	100.0 (27/27)	100.0 (65/65)

[1)] After 7 days administration: end of treatment
Eradication（%）＝number of eradications/number of total ×100

higher, less than 5.0 mg/kg）twice daily for 7 days, and CDTR-PI was orally administered at the high dose（one time dose of 4.2 mg/kg or higher, less than 6.0 mg/kg）three times daily for 7 days.

S. pneumoniae was detected as causative organism in 31 subjects of TBPM-PI administration group, and 33 subjects of CDTR-PI administration group. *H. influenzae* was detected as causative organism in 33 subjects of TBPM-PI administration group, and 28 subjects of CDTR-PI administration group. According to sensitivity distribution against all possible causative organisms in this clinical trial, MIC_{90} of TBPM and CDTR was both 0.5 μg/mL. In the TBPM-PI administration group 3 days after the start of administration, the eradication rate was 100%（27/27）for *S. pneumoniae* and 96%（24/25）for *H. influenzae*. In the same group after the administration finalized, the eradication rate was 100%（31/31）for *S. pneumoniae* and 100%（69/69）for *H. influenzae*. In the CDTR-PI administration group 3 days after the start of administration, the eradication rate was 64%（21/33）for *S. pneumoniae* and 100%（27/27）for *H. influenzae*. In the same group after the administration finalized, the eradication rate was 97%（30/31）for *S. pneumoniae* and 100%（65/65）for *H. influenzae*.

Results

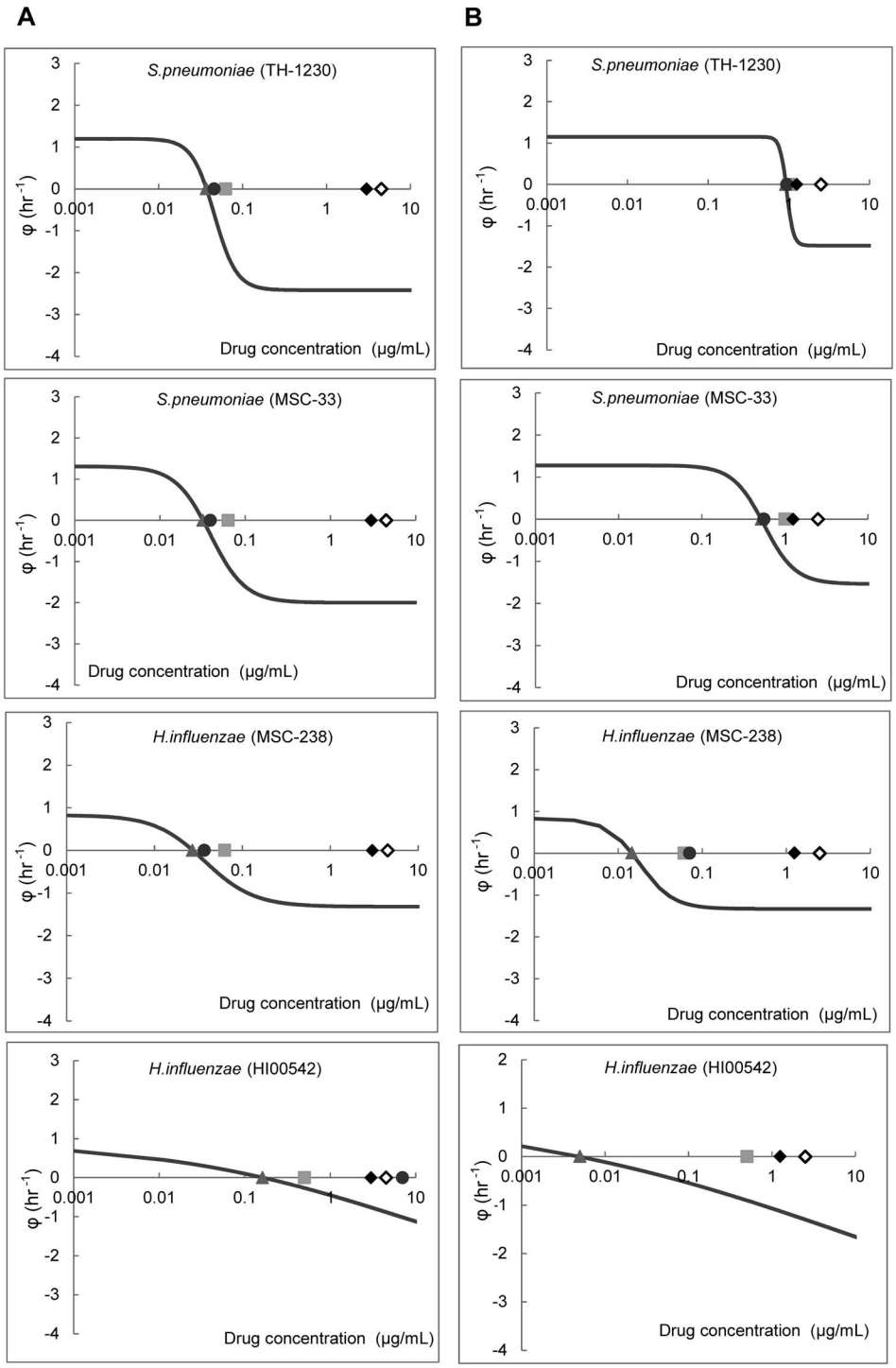
Dynamic PD parameters and PD characteristics

The interaction between the φ and drug concentrations（φ curve）is shown in Fig. 2 to examine the PD characteristics of TBPM and CDTR against each bacterial strain.

1） TBPM

The maximum bactericidal activity（φ_{max}）was from −2 to −3, and $t_{1/10}$ was about 1 hour based on the φ curve for *S. pneumoniae*（PRSP: TH-1230, MSC-33）. Bactericidal effects were noted to be enhanced along with increased drug concentrations, but the bactericidal effects would be leveled off at around C_{max}.

Fig. 2. Interaction between concentrations of TBPM or CDTR and their antimicrobial activities against *S. pneumoniae* and *H. influenzae*



A: TBPM-PI, B: CDTR-PI

▲: SC, ■:MIC, ●: EC_{50}, ◆: C_{max}（TBPM-PI; 4 mg/kg, CDTR-PI; 3 mg/kg）, ◇: C_{max}（TBPM-PI; 6 mg/kg, CDTR-PI; 6 mg/kg）

On the other hand, the φ curve for *H. influenzae*（BLNAS:MSC-238）indicated that the maximum bactericidal activity（φ_{max}: −1.3）for *H. influenzae* was smaller than that for *S. pneumoniae*. The $t_{1/10}$ was 1.7 hours. That is to say, the bactericidal activity of TBPM-PI was shown to be *S. pneumoniae*（PRSP）＞*H. influenzae*（BLNAS）. Bactericidal effects were noted to be enhanced along with increased drug concentrations, but to be leveled off at around C_{max}. In addition, the φ curve for BLNAR（HI00542）showed enhanced bactericidal activity along with increased drug concentrations within the clinical plasma concentration range（dose: 6 mg/kg, C_{max}: 4.5 μg/mL）. The $t_{1/10}$ was 0.7 hour.

2） CDTR

The φ curve for *S. pneumoniae*（PRSP: TH-1230）indicated that φ_{max} value was about −1.5, and $t_{1/10}$ value was 1.5 hours. Along with increased drug concentrations, the bactericidal activity became outstandingly noticeable at around MIC, and it would not be enhanced any more even though the concentration was increased.

On the other hand, the φ curves for *S. pneumoniae*（PRSP: MSC-33）and *H. influenzae*（BLNAS: MSC-238）indicated that φ_{max} values were about −1.5, and $t_{1/10}$ was about 1.5 hours. The bactericidal activity was shown to be enhanced along with increased drug concentrations. The bactericidal activity against *H. influenzae*（BLNAS: MSC-238）was leveled off at around C_{max}.

Furthermore, in the φ curve for *H. influenzae*（BLNAR: HI00542）, enhancement of bactericidal activity was noted along with increased drug concentrations within the clinical plasma concentration range（dose: 6 mg/kg, C_{max}: 2.5 μg/mL）. The $t_{1/10}$ was 0.54 hour.

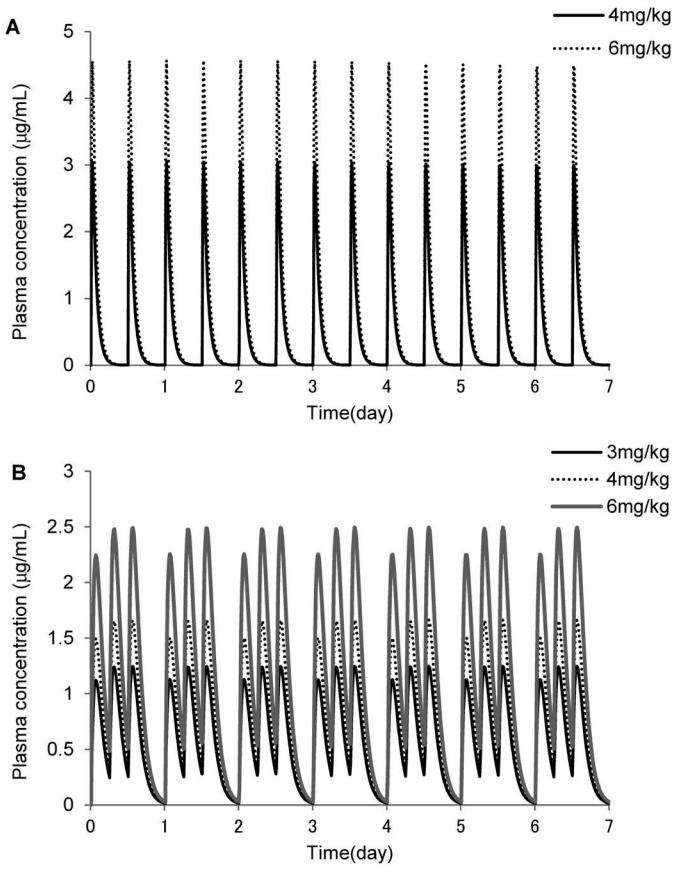
Simulation of plasma concentrations

Plasma concentrations were simulated in the following dosage regimens set up by using PPK parameters of TBPM-PI and CDTR-PI（Fig. 3）.

1） TBPM-PI, 4 mg/kg×2/day, 7 days repeated dose
2） TBPM-PI, 6 mg/kg×2/day, 7 days repeated dose
3） CDTR-PI, 3 mg/kg×3/day, 7 days repeated dose
4） CDTR-PI, 4 mg/kg×3/day, 7 days repeated dose
5） CDTR-PI, 6 mg/kg×3/day, 7 days repeated dose

C_{max} of TBPM was about 3 μg/mL at static condition after repeated dosing of TBPM-PI at one time dose of 4 mg/kg twice daily, and it was 4.5 μg/mL at 6 mg/kg twice daily. On the other hand, when CDTR-PI was administered at one time dose of 3 mg/kg three times daily, C_{max} at static condition was about 1.25 μg/mL, and it was about 1.7 μg/mL at 4 mg/kg and about 2.5 μg/mL at 6 mg/kg.

Fig. 3. Plasma concentration simulations of TBPM or CDTR after oral administration of TBPM-PI or CDTR-PI in child using their population mean parameters



A: TBPM-PI; 2 times/day×7 days, B: CDTR-PI; 3 times/day×7 days

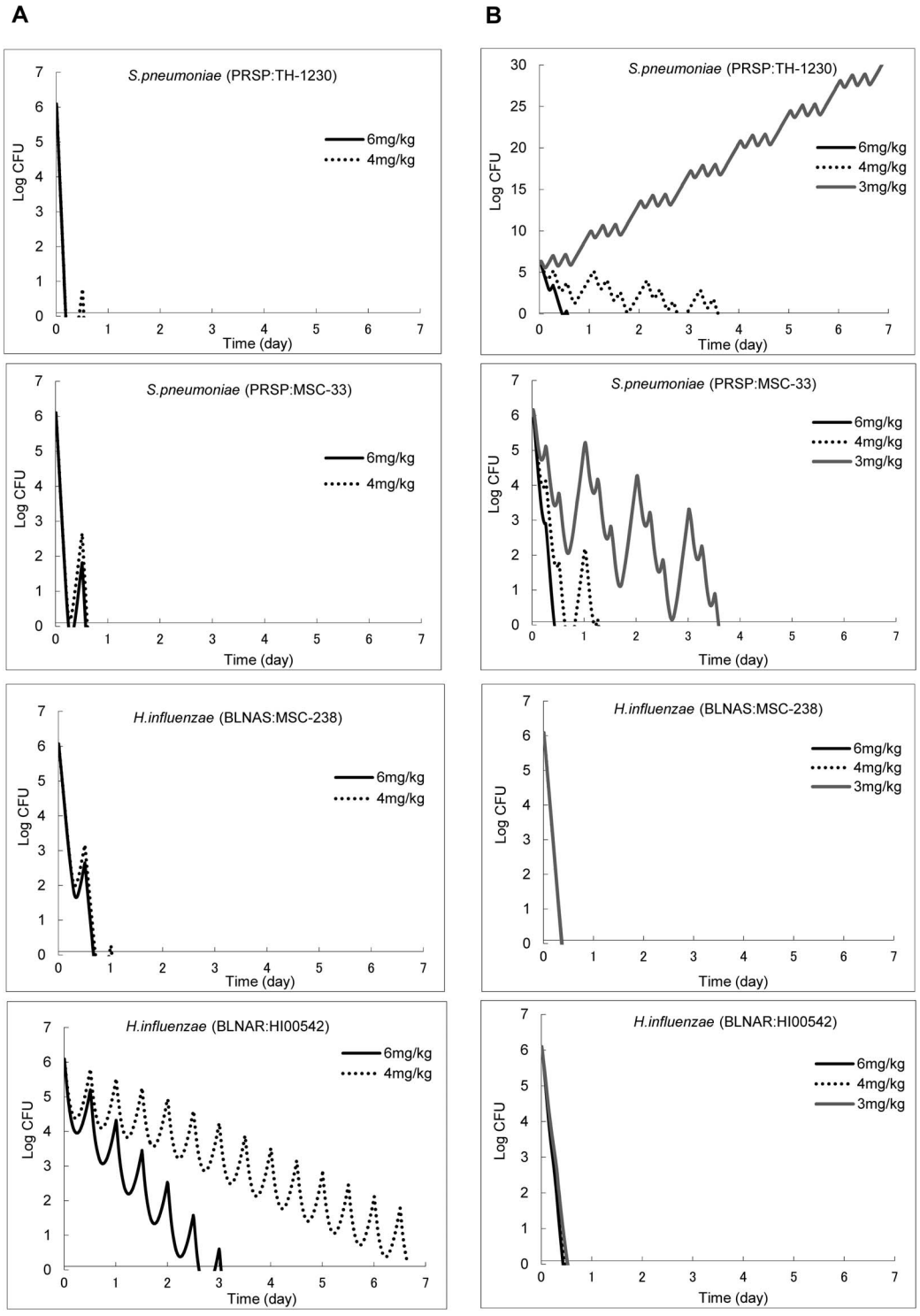
Simulated time-course profiles of viable bacterial counts *in vivo*

The time-course profile of *in vivo* bacterial counts was simulated for each bacterial strain by introducing estimated plasma concentration profiles of TBPM and CDTR into Eq1. The results are shown in Fig. 4.

1） TBPM

TBPM-PI administration at 4 mg/kg and 6 mg/kg rapidly decreased *in vivo* bacterial counts of *S. pneumoniae*（PRSP: TH-1230, MSC-33）and *H. influenzae*（BLNAS: MSC-238）, and completely eradicated those within one day or so after the administration initiated. On the contrary, in the case of *H. influenzae*（BLNAR: HI00542）, TBPM-PI administration at 4 mg/kg decreased *in vivo* bacterial counts slowly, and some microorganisms were expected to be viable even 7 days after the start of administration. TBPM-PI at 6 mg/kg, however, seemed to eradicate the microorganisms completely on 4 days after the start of administration.

Fig. 4. Predicted time-course profiles of viable bacterial counts *in vivo*



A: TBPM-PI; 2 times/day×7 days, B: CDTR-PI; 3 times/day×7days

2） CDTR

CDTR-PI administration at 3 mg/kg decreased *in vivo* bacterial counts of *S. pneumoniae*（PRSP: MSC-33）relatively slowly, and complete eradication was expected to be on 4 days after the administration initiated. By increasing the dose level from 4 mg/kg to 6 mg/kg, one or 2 days administration seemed to be enough for eradication of microorganisms. In the case of *S. pneumoniae*（PRSP: TH-1230）, CDTR-PI administration at 3 mg/kg did not decrease but increase *in vivo* bacterial counts. By increasing the dose level to 4 mg/kg or 6 mg/kg, the *in vivo* bacterial counts turned to be decreasing. Complete eradication of microorganisms seemed to require CDTR-PI administration at 4 mg/kg for at least 4 days or the administration at 6 mg/kg for 1 day or longer. In the case of *H. influenzae*（BLNAS: MSC-238, BLNAR: HI00542）, the *in vivo* bacterial counts were decreased rapidly at any dose levels（3～6 mg/kg）, and complete eradication of microorganisms was expected to be within one day after the start of administration.

Discussion

In this study, we examined the PD specific characteristics of TBPM and CDTR against *S. pneumoniae* and *H. influenzae* major causative pathogens for pediatric respiratory infections, and estimated the *in vivo* bacterial count profiles in the administration under clinical dosage regimen using a mechanism-based PK-PD model.

PD characteristics

According to the criteria established by Sato *et al.* and the φ curve（Fig. 2）, the PD characteristics of TBPM against *S. pneumoniae*（PRSP: TH-1230, MSC-33）and *H. influenzae*（BLNAS: MSC-238, BLNAR: HI00542）as well as those of CDTR against *S. pneumoniae*（PRSP: MSC-33）and *H. influenzae*（BLNAS: MSC-238, BLNAR: HI00542）were considered to be concentration-dependent and also time-dependent. On the other hand, the PD characteristics of CDTR against *S. pneumoniae*（PRSP: TH-1230）was assumed to be “time-dependent”, which suggested that antibiotics have different PD characteristics against different strains of the same bacterial species.

Simulation of *in vivo* bacterial counts and clinical bacteriological effects

1） TBPM

The stationary concentrations（SC）of TBPM against *S. pneumoniae*（PRSP: TH-1230, MSC-33）and *H. influenzae*（BLNAS: MSC-238）were 0.03～0.04 μg/mL, and the C_{max} of clinical plasma concentrations（dose: 4 mg/kg; 3 μg/mL, dose: 6 mg/kg; 4.5 μg/mL）was about 100 times the SC（Fig. 2）. According to the SC and φ_{max} value, TBPM-PI was expected to exert high efficacy against *S. pneumoniae* and *H. influenzae*（BLNAS）at clinical dosages. Simulation

results of *in vivo* bacterial counts also projected a very rapid decrease of *S. pneumoniae*（TH-1230, MSC-33）and *H. influenzae*（MSC-238）after repeated oral administration of TBPM-PI at 4 mg/kg and 6 mg/kg, and complete eradication within one day after the start of administration（Fig. 4-A）. The bacteriological results in clinical trials（Table 3）supported this simulation in which the eradication rates of *S. pneumoniae* and *H. influenzae* were almost 100% 3 days after the start of administration.

On the other hand, the SC of TBPM against *H. influenzae*（BLNAR: HI00542）was 0.075 μg/mL, and C_{max} of clinical plasma concentrations（dose: 4 mg/kg; 3 μg/mL, dose: 6 mg/kg; 4.5 μg/mL）largely exceeded the SC. However, γ was significantly small as 0.29. Even though the concentration was raised within the range of clinical plasma concentrations, it did not reach to φ_{max} and the φ at around C_{max} was about -1. The simulation results of *in vivo* bacterial counts suggested the degree of decrease in the count of *H. influenzae*（BLNAR: HI00542）was significantly different depending on dose levels of 4 mg/kg and 6 mg/kg in repeated oral administration of TBPM-PI. That is to say, TBPM exerts its efficacy “concentration-dependently” against *H. influenzae*（BLNAR: HI00542）, and higher dose level gives stronger bactericidal activity, which supports the result of bacterial eradication by raising the dose level from 4 mg/kg to 6 mg/kg（Fig. 4-A）.

2） CDTR

The SCs of CDTR against *S. pneumoniae*（PRSP: TH-1230, MSC-33）were 0.9 and 0.5 μg/mL, and the C_{max} of clinical plasma concentrations（dose: 6 mg/kg; 2.5 μg/mL）was 2.8 and 5 times the SCs, respectively. Simulation results of *in vivo* bacterial counts predicted complete eradication of microorganisms within 1～4 days after the start of administration of CDTR-PI at 4～6 mg/kg（Fig. 4-B）. The bacteriological effect results of clinical trials（Table 3）supported the eradication ratio of *S. pneumoniae* at 96.8% on 7 days after the start of CDTR-PI administration.

On the other hand, the SCs of CDTR against *H. influenzae*（BLNAS: MSC-238 and BLNAR: HI00542）were 0.015 and 0.005 μg/mL, and the C_{max} of clinical plasma concentrations（dose: 6 mg/kg; 2.5 μg/mL）was 100 times the SC or higher. The SCs and φ_{max} values suggested that CDTR-PI exerts its high efficacy on *H. influenzae*（BLNAS and BLNAR）at clinical doses. Simulation results of *in vivo* bacterial counts predicted a rapid decrease in *in vivo* counts of *H. influenzae*（BLNAS and BLNAR）at both doses of 4 mg/kg and 6 mg/kg, and complete eradication of microorganisms within the first day of CDTR-PI administration（Fig. 4-B）. The bacteriological effect results in clinical trials supported almost 100% eradication ratio of *H. influenzae* on 3 days after the start of CDTR-PI administration（Table 3）.

As mentioned in the above, the *in vivo* bacterial counts predicted on the basis of mechanism-based PK-PD approach were well correspondent to the bacteriological efficacy results in clinical trials.

The present study allowed us to profoundly investigate the PD characteristics of TBPM and

CDTR against *S. pneumoniae* and *H. influenzae*, and predict the clinical bacteriological efficacy of those. We recognized, however, the existence of resistant strains that are hardly eradicated at the ordinary clinical doses in cases of TBPM against *H. influenzae*（BLNAR: HI00542）and CDTR against *S. pneumoniae*（PRSP: TH-1230）. Owing to the analysis of PD characteristics, we now understand increased one-time dosage of up to 6 mg/kg would be effective for both TBPM-PI and CDTR-PI.

The present study revealed that the PD characteristics of an antibiotic differ depending on bacterial species and strains. We would like to further deepen our discussions on other bacterial species and strains as well. In addition, it is also considered to be very crucial to examine the clinical bacteriological efficacy using other antibiotics for the purpose of confirming appropriateness of mechanism-based PK-PD approach.

Conclusion

In vitro bactericidal curve was analyzed using the mechanism-based PK-PD model, and the PD characteristics of TBPM and CDTR against *S. pneumoniae* and *H. influenzae* were clarified on the basis of dynamic PD parameters obtained. In addition, the simulation results of *in vivo* bacterial counts after administration in the clinical dosage regimen were well correspondent to the bacteriological efficacy results in clinical settings. Accordingly, mechanism-based PK-PD approach was considered to be beneficial to predict *in vivo* clinical bacteriological efficacy.

Conflict of interest

The authors declare no conflict of interest.

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