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Prostatic pharmacokinetic/pharmacodynamic evaluation of ampicillin-sulbactam for bacterial prostatitis and preoperative prophylaxis

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Abstract

This study aims to define the penetration of ampicillin and sulbactam into prostate tissue, develop a prostatic pharmacokinetic model of each drug and assess the appropriateness of ampicillin-sulbactam regimens for the treatment of prostatitis and the prophylaxis of postoperative infection, based on a pharmacokinetic and pharmacodynamic simulation. Subjects were prostatic hyperplasia patients prophylactically receiving a 0.5-h infusion of 1.5 g (1 g:0.5 g) or 3 g (2 g:1 g) ampicillin-sulbactam before transurethral resection of the prostate. Ampicillin and sulbactam concentrations in plasma and prostate tissue were measured. The prostate tissue/plasma ratios of both ampicillin and sulbactam were approximately 0.37 (area under the drug concentration-time curve) and penetration was similar. The prostatic population pharmacokinetic model, included a covariate analysis, adequately predicted prostate tissue concentrations in our patient population. For therapeutic use, aiming for a bactericidal target of 50% of time above minimum inhibitory concentration (T > MIC) in prostate tissue, 3 g ampicillin-sulbactam four times daily achieved ≥90% expected

probability against only *E. faecalis* in typical patients with a creatinine clearance (CL_{cr}) = 30 mL/min. For prophylactic use, aiming for a bacteriostatic target of 30% T > MIC, 3 g ampicillin-sulbactam four times daily achieved ≥90% expected probability of attaining the bacteriostatic target against *E. faecalis* and *Proteus* species when CL_{cr} = 30 mL/min. Based on prostatic simulations, the present study provides helpful recommendations for the treatment of bacterial prostatitis and preoperative prophylaxis in prostatectomy.

Keywords: ampicillin, sulbactam, pharmacokinetics, pharmacodynamics, bacterial prostatitis, prostatectomy

Introduction

Ampicillin-sulbactam is an antimicrobial combination comprising ampicillin, a β-lactam antimicrobial agent, and sulbactam, a β-lactamase inhibitor, blended at a dose ratio of 2:1. A dose adjustment based on renal function is recommended, since both drugs are excreted renally.[1,2] Ampicillin-sulbactam has antibacterial activity against gram-positive and gram-negative bacteria, and has been used for urinary tract infection (UTI) and antibacterial prophylaxis in urological surgery.[2-5]

Bacterial prostatitis, which is classified as a UTI, is caused by infection with uropathogens; mainly gram-negative bacteria such as *Escherichia coli*, although infection is sometimes due to gram-positive bacteria such as *Enterococcus* species. Ampicillin has previously been used to treat bacterial prostatitis due to *Enterococcus* species.[5-7] However, the effectiveness of ampicillin-sulbactam for the treatment of prostatitis and the optimal dosage for prostatitis and prophylactic administration in prostatectomy remain unclear.

From the perspective of pharmacokinetic/pharmacodynamic (PK/PD) theory, the antimicrobial activity of β-lactam antimicrobial agents such as ampicillin is generally

dependent on the exposure time during which the plasma drug concentrations remain above the minimum inhibitory concentration for the bacterium (T > MIC).[8,9] However, antimicrobial agents act at the site of infection rather than in the plasma. Therefore, it is important to understand the PK of ampicillin-sulbactam in prostate tissue to assess its effectiveness in the treatment of bacterial prostatitis and the prevention of postoperative infection.

Several previous reports concerning ampicillin-sulbactam penetration into human prostate,[10] as well as into other sites, including human epididymis and testis,[11] lung tissue,[12] human costal cartilage,[13] and peritoneal fluid,[14] have been published. However, none of the previous reports has described PK at these sites or assessed site-specific PK/PD with mathematical modeling and stochastic simulation.

In this paper, we aim to characterize the prostatic population PK of ampicillin and sulbactam and to evaluate ampicillin-sulbactam site-specific PK/PD target attainment. Furthermore, this paper discusses individualized dosing regimens of ampicillin-sulbactam for bacterial prostatitis and preoperative prophylaxis in prostatectomy.

Materials and Methods

Study design and subjects

This study was an open label, non-comparative and prospective study at Aichi Medical University Hospital and its related facilities in Japan. Subjects were male patients with prostatic hyperplasia prophylactically receiving a 0.5-h infusion of 1.5 g ampicillin-sulbactam (1.0 g : 0.5 g) or 3.0 g ampicillin-sulbactam (2.0 g : 1.0 g) before transurethral resection of the prostate (TURP). The study protocol was reviewed and approved by the ethics committee (Aichi Medical University School of Medicine). Samples were collected from patients who had given written informed consent. Patients who were hypersensitive to β-lactams were excluded.

Drug administration and sample collection

Ampicillin-sulbactam (1.5 g or 3.0 g) was administered preoperatively by a 0.5-h intravenous infusion. Blood samples were scheduled to be drawn 0.5, 1, 1.5, 3, and 5 h after preoperative drug administration. Blood samples were centrifuged immediately

after collection, and plasma was obtained. Prostate tissue samples were scheduled to be collected during TURP 0.5, 1, and 1.5 h after the start of the infusion. The resected prostate was washed with chilled physiological saline. All plasma and prostate samples were stored at –40°C until analyzed.

Measurement of ampicillin and sulbactam concentrations in plasma and prostate samples

The concentrations of ampicillin and sulbactam in the plasma and prostate samples were analyzed by high-performance liquid chromatography (HPLC) according to the methods of Martin *et al*. and Bawdon *et al*. (with minor modifications).[15,16] For ampicillin, prostate tissue samples (0.5 g) were homogenized using an overhead mixer with two volumes (1 mL [w/v]) of double distilled water. The prostate tissue homogenate was centrifuged, and the supernatant was collected for further processing. The tissue supernatants or plasma samples (200 μL each) were then added to 200 μL of acetonitrile, and the mixture was vortexed and centrifuged. Next, the supernatants (300 μL) were added to 900 μL dichloromethane and the mixture was vortexed and

centrifuged. 20 μL of the supernatants were injected into the HPLC system. The HPLC employed a C18 column (Waters XBridge C18 5 μm 4.6 × 150 mm) at a temperature of 40°C and ampicillin detection was at 219 nm. The mobile phase consisted of a mixture of 10 mmol/L potassium phosphate buffer (pH 4.7) and acetonitrile (98:2 [v/v]) with a flow rate of 1.6 mL/min. The quantification limits for ampicillin were 0.30 μg/mL and 1.5 μg/g in plasma and prostate tissue, respectively. The calibration curves were linear up to 300 μg/mL (plasma) and 150 μg/g (prostate tissue).

For sulbactam, the analysis methods were similar to those described above. Tissue supernatants or plasma samples (200 μL each) were added to 100 μL of 2.5 mmol/L imidazole and 400 μL of acetonitrile. The supernatants (500 μL) were added to 600 μL dichloromethane. The HPLC employed a C18 column at a temperature of 25°C and sulbactam detection was at 322 nm. The mobile phase consisted of a mixture of 0.1 mol/L potassium phosphate buffer (pH 6.1) and acetonitrile (98:2 [v/v]) with a flow rate of 1.0 mL/min. The quantification limits for sulbactam were 0.15 μg/mL and 0.75 μg/g in plasma and prostate tissue, respectively. The calibration curves were linear up to 150 μg/mL (plasma) and 75 μg/g (prostate tissue).

For each drug, the interday and intraday accuracy (as absolute values of relative errors of the means) and precision (as coefficients of variations) were within 10%.

Non-compartmental pharmacokinetic analysis

For each drug, C_{max} was defined as the observed maximum concentration of individual subjects, and the C_{max} values were calculated as their mean and standard deviation. The area under the drug concentration-time curve from 0 to infinity (AUC) of individual subjects was estimated as the actual area from 0 to 1.5 h ($AUC_{0–1.5h}$) plus the extrapolated area ($AUC_{1.5h–\infty} = C_{1.5h}/\lambda_Z$, where $C_{1.5h}$ is the drug concentration at 1.5 h and λ_Z is the terminal slope on a $\log_e$ scale) based on the trapezoidal rule. Thus, subjects who provided only one sampling timepoint were excluded from this AUC estimation. The estimated AUC values were expressed as their mean and standard deviation. The drug penetration ratio into prostate tissue was defined as the C_{max} or AUC ratio; frequently used indices of drug distribution into tissues. The specific gravity of prostate tissue was defined as 1 (g = mL).

Population pharmacokinetic modeling

The population pharmacokinetics of ampicillin and sulbactam were described using the following hybrid model (Figure S1) separately for each drug.

$$dX(central)/dt = R_{inf} - (CL/V_{central} + Q/V_{central}) * X(central) + Q*X(peripheral)/V_{peripheral}$$

$$dX(peripheral)/dt = Q*X(central)/V_{central} - Q*X(peripheral)/V_{peripheral}$$

$$dX(prostate)/dt = Q_{prostate}*X(central)/V_{central} - Q_{prostate}*X(prostate)/V_{prostate}/KP_{prostate}$$

where X(central), X(peripheral), X(prostate) are the amounts of drug (mg) in the central, peripheral, and prostate compartments, respectively; R_{inf} is rate of infusion (mg/h); CL is the clearance (L/h) from the central compartment; $V_{central}$ and $V_{peripheral}$ are the volumes of distribution (L) of the central and peripheral compartments, respectively; and Q is the

central-peripheral intercompartmental clearance (L/h). We also used $KP_{prostate}$ (prostate-to-plasma partition coefficient), $Q_{prostate}$ (prostatic plasma flow in L/h), and $V_{prostate}$ (prostatic volume in L) as physiological parameters. $KP_{prostate}$ was calculated by non-compartmental pharmacokinetic analysis. $Q_{prostate}$ and $V_{prostate}$ were quoted from the literature.[17,18] Population pharmacokinetic modeling was performed using the NONMEM program (version 7.4; ICON Public Limited Company, Dublin, Ireland).

For population PK modeling, the fixed-effects parameters were CL, $V_{central}$, Q, $V_{peripheral}$, $KP_{prostate}$, $Q_{prostate}$ and $V_{prostate}$. The interindividual variability was modeled with an exponential error model: $\theta_i = \theta*\exp(\eta_i)$, where θ_i is the fixed-effects parameter for the i-th subject, θ is the mean value of the fixed-effects parameter in the population, and η is a random interindividual variable, which is normally distributed with mean zero and variance ω^2. The residual variability was modeled with an additive error model: $C_{obs,\,ij} = C_{pred,\,ij} + \varepsilon_{ij}$, where $C_{obs,\,ij}$ and $C_{pred,\,ij}$ denote the j-th observed and predicted concentrations for the i-th subject, and ε is a random intraindividual error, which is normally distributed with mean zero and variance σ^2.

A covariate test was performed to develop the final model. Age, body weight, blood urea nitrogen (BUN), creatinine clearance (CL_{cr}), total bilirubin (T-Bil), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were tested for covariates of CL, and body weight for covariates of volume of distribution. These candidates were incorporated into the covariate model based on the statistical significance (Table S1). Creatinine clearance was calculated with the Cockcroft & Gault equation.[19] The covariates model was expressed as follows:

$$CL_{i(k)} = CL_{(k)} * (x_i / \text{median}(x))^{\theta x}$$

where $CL_{i(k)}$ represents the model predicted parameter for analyte k (1 for ampicillin and 2 for sulbactam) for the typical individual i with covariate x_i. $CL_{(k)}$ represents the population central tendency for the individual $CL_{i(k)}$. The median(x) represents the median value for the covariate in the subjects and θ_x represents a scale factor.

Model qualification

To assess the reliability and stability of the estimated parameters, a nonparametric bootstrap method was performed using Perl-speaks-NONMEM software.[20] The 95% confidence intervals of the parameters from 1000 bootstrap replicates were compared with the estimates of the final population model. The adequacy of the final population model was qualified by diagnostic scatter plots. Visual predictive checks were also performed to qualify the final model. One thousand data sets were simulated using the final parameter estimates including the interindividual and residual variability, and the simulation was prediction-corrected for both lower and higher doses.[20]

Pharmacokinetic/pharmacodynamic simulation

A set of fixed-effects parameters θ_i (CL, $V_{central}$, Q, $V_{peripheral}$, $KP_{prostate}$, $Q_{prostate}$, and $V_{prostate}$) for ampicillin and sulbactam were randomly generated 1000 times by $SIMULATION command in NONMEM, according to each mean estimate and interindividual variance of the developed model. The set of seven θ_i values gave hybrid model equations and simulated ampicillin and sulbactam concentrations in plasma and

prostate tissue. The time point at which the drug concentration coincided with a specific minimum inhibitory concentration (MIC) value (0.25-64 μg/mL) was determined, and the drug exposure time above the MIC for bacteria (T > MIC) was calculated as the cumulative percentage of 24 h for different renal function and different dosing intervals. In plasma, the unbound drug concentration was simulated using the fixed-effects parameters, where a value of 72% non-protein binding rate (the free fraction *f*) of ampicillin was used.[1] On the other hand, in prostate tissue, the total concentration was not adjusted for the free fraction because the protein binding of ampicillin and sulbactam in the prostate are currently unknown. Even a moderately higher or lower protein binding in the prostate compared to serum was not considered to significantly affect this simulation.

The probability of target attainment (%) at a specific MIC in plasma and prostate tissue was defined as the proportion that achieved 30% *f*T > MIC and 30% T > MIC (bacteriostatic target) or 50% *f*T > MIC and 50% T > MIC (bactericidal target) of 1000 estimates.[21,22] The probability at a specific MIC was then multiplied by the fraction of clinical isolate population at each MIC category, and the sum of individual products was determined as the expected population probability (empirical use; assuming that

causative bacteria is uncertain) of attaining pharmacodynamic target in prostate tissue (%). MIC distributions against common bacteria causing prostatitis were derived from MIC distributions for "ampicillin-sulbactam (ratio)" in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database.[23] The MICs for 50th percentile (MIC_{50}) of the clinical isolates were 8 μg/mL for *Escherichia coli*, 4 μg/mL for *Klebsiella* species, 2 μg/mL for *Proteus* species, 1 μg/mL for *Enterococcus faecalis*, 32 μg/mL for *Enterococcus faecium*, and 64≤ μg/mL for *Pseudomonas aeruginosa*, respectively.

Results

Characteristics of the subjects

The demographic parameters (mean ± standard deviation) of the study subjects in the ampicillin-sulbactam 1.5 g (n = 22) and 3.0 g (n = 22) groups are shown in Table 1. The subjects had no large abnormality on the laboratory data.

Non-compartmental pharmacokinetic analysis

The non-compartmental PK parameters are summarized in Table 2, as several subjects were excluded when their PK parameters were not estimated due to lack of sampling timepoint. For the lower dose group, the mean C_{max} values (ampicillin and sulbactam) were 72.6 and 36.5 μg/mL in plasma, and 22.8 and 12.4 μg/g in prostate tissue. The mean AUC values (ampicillin and sulbactam) were 102.6 and 56.6 μg·h/mL in plasma, and 32.9 and 21.7 μg·h/g in prostate tissue. For the higher dose group, the mean C_{max} values (ampicillin and sulbactam) were 155.0 and 62.9 μg/mL in plasma, and 44.2 and 20.9 μg/g in prostate tissue. The mean AUC values (ampicillin and sulbactam)

were 208.2 and 96.7 μg·h/mL in plasma, and 65.3 and 30.1 μg·h/g in prostate tissue. C_{max} and AUC values in prostate tissue increased when doubling the dose, similar to that observed in plasma, showing dose linearity in the prostatic pharmacokinetics of ampicillin and sulbactam.

For the lower ampicillin-sulbactam group, the mean prostate tissue/ plasma ratios were 0.33-0.37 in C_{max} and 0.43-0.42 in AUC. For the higher ampicillin-sulbactam group, the mean prostate tissue/ plasma ratios were 0.29-0.34 in C_{max} and 0.35-0.35 in AUC. In AUC, the mean prostate tissue/ plasma ratio of ampicillin and sulbactam was in the range of 0.35 to 0.43.

The ampicillin/ sulbactam ratio of C_{max} and AUC in prostate tissue was about 2:1 regardless of the dose.

Population pharmacokinetic modeling

All ampicillin and sulbactam concentration-time data (219 plasma samples, 109 prostate samples) were adequately fit to the hybrid models. The final parameters of

ampicillin and sulbactam in this model are listed in Table 3. Incorporation of CL_{cr} into CL caused the largest change in the objective function (Table S1) and median CL_{cr} (68.3 mL/min) was used. None of the examined covariates had a significant effect on $V_{central}$, Q, or $V_{peripheral}$. For both drugs, the physiological fixed-effects parameters were fixed as $KP_{prostate} = 0.37$, $Q_{prostate} = 0.311$ L/h,[17] and $V_{prostate} = 0.05$ L.[18] All the parameter estimates including the interindividual and intraindividual variability were all in the range of the 95% confidence intervals obtained using the bootstrap method.

The diagnostic scatter plots are represented in Figure 1. For both plasma and prostate tissue, plots of observed plasma concentration (DV) *vs.* population predicted concentration (PRED) and individual predicted concentration (IPRED) indicated no major bias. For both plasma and prostate tissue, plots of conditional weighted residual (CWRES) *vs.* PRED and time did not show any systematic trend, where the CWRES values were within ±3 (= 99% confidence interval). Prediction-corrected visual predictive checks were also performed for observed and predicted concentrations (based on the final model) of ampicillin and sulbactam vs. time (Figure 2). The observed concentrations at 10, 50, and 90th percentile points were within the predicted 90% confidence intervals for 10, 50, and 90th percentile points. Overall, the final model

adequately described pharmacokinetics of ampicillin and sulbactam in plasma and prostate tissue.

Pharmacokinetic and pharmacodynamic evaluation

The probabilities of attaining bacteriostatic and bactericidal targets in plasma and prostate tissue using different ampicillin-sulbactam regimens, at specific MICs, are shown in Figure 3. The probability-MIC curve of prostate tissue showed a leftward shift as compared with that of plasma. This result indicates the probabilities of attaining site-specific PK/PD targets in prostate tissue (Figure 3B) were lower than the probabilities in plasma (Figure 3A). The site-specific PK/PD breakpoint MIC (the highest MIC at which the target-attainment probability in prostate tissue was ≥90%) values were represented in Table 4. Regarding the bacteriostatic target of 30% T > MIC in typical patients with CL_{cr} = 60 mL/min, the site-specific PK/PD breakpoint MIC were as follows: 0.25 μg/mL for 1.5 g (total ampicillin-sulbactam) twice daily; 0.5 μg/mL for 3.0 g twice daily; 1 μg/mL for 1.5 g three times daily; 2 μg/mL for 3.0 g three times daily and 1.5 g four times daily; 4 μg/mL for 3.0 g four times daily. Regarding the

bactericidal target of 50% T > MIC in typical patients with CL_{cr} = 60 mL/min, the site-specific PK/PD breakpoint MIC values were as follows: 0.25 μg/mL for 1.5 g three times daily; 0.5 μg/mL for 3.0 g three times daily and 1.5 g four times daily; 1 μg/mL for 3.0 g four times daily.

The expected probabilities of site-specific pharmacodynamic target attainment, against bacterial populations of *E. coli*, *Klebsiella* species, *Proteus* species, *E. faecalis*, *E. faecium*, and *P. aeruginosa* isolates are shown in Table 5. The probabilities of target attainment values basically increased in the follow order: 1.5 g twice daily < 3.0 g twice daily < 1.5 g three times daily < 1.5 g four times daily and 3.0 g three times daily < 3.0 g four times daily; CL_{cr} of 90 mL/min < 60 mL/min < 30 mL/min in typical patients. For 50% T > MIC bactericidal activity, dosing regimens which indicate the expected probability was ≥90% against *E. faecalis* were only 1.5 g four times daily, 3.0 g three times daily, and 3.0 g four times daily, in typical patients with 30 mL/min. For 30% T > MIC bacteriostatic activity, in patients with a CL_{cr} of 30 mL/min all dosing regimens resulted in an expected probability of ≥90% against *E. faecalis*, whereas in patients with a CL_{cr} of 60 or 90 mL/min, only some regimens did. For *Proteus* species, in patients

with a CL_{cr} of 30 mL/min, the expected probability of ≥90% was obtained only with the regimen of 3.0 g four times daily.

Discussion

This study examined the prostatic pharmacokinetics of both ampicillin and sulbactam in patients with prostatic hyperplasia and identified the penetration of each drug into prostate tissue. This study also described hybrid modeling of each drug concentration in plasma and prostate tissue and performed a stochastic site-specific PK/PD simulation based on this model. Furthermore, from the results of this simulation, we assessed the appropriateness of ampicillin-sulbactam regimens for the treatment of prostatitis and the prophylaxis of postoperative infection by each renal function (CL_{cr} = 30, 60, 90 mL/min). In patients with CL_{cr} = 30 mL/min, regimens of 3 g ampiciliin-sulbactam four times daily (12 g/day) achieved ≥90% expected probability against only *E. faecalis* for 50% T > MIC target but against both. *E. faecalis* and *Proteus* species for 30% T > MIC target.

In the non-compartmental PK analysis, the mean prostate tissue/plasma C_{max} ratios of ampicillin and sulbactam were 0.31 and 0.36, respectively. The mean prostate tissue/plasma AUC ratios of ampicillin and sulbactam were 0.37 and 0.37, respectively. For both drugs, the penetration from the systemic circulation into the prostate tissue was

about the same in this study. Klotz *et al*. reported the ranges of ampicillin and sulbactam prostatic concentration in patients with benign prostatic hypertrophy were 0.42-548.3 μg/g and 0.20-249.7 μg/g, respectively, at 15-55 min after a single infusion over 15 min of 2 g ampicillin and 1 g sulbactam.[10] Our data indicated the ranges of ampicillin and sulbactam prostatic concentration were 16.5-88.6 μg/g and 11.8-41.8 μg/g at 30 min, respectively, and 5.2-62.7 μg/g and 4.0-19.3 μg/g at 60 min, after a single infusion of 2 g ampicillin and 1 g sulbactam. Our prostatic concentrations were within the range of Klotz *et al*. The mean ampicillin/ sulbactam ratio in the prostate tissue (C_{max} 1.83-2.01, AUC 1.67-2.24) was also about the same as plasma (C_{max} 2.03-2.42, AUC 1.81-2.12). It has been reported that the ampicillin/ sulbactam ratio which indicates the most effective antibacterial activity was 1.0 to 2.0.[24] Therefore, it is assumed that antibacterial activity is maintained in prostate tissue as well as plasma. Also, considering that the mean ampicillin/sulbactam ratio in prostate tissue was around 2, the use of MIC values for ampicillin-sulbactam (2:1) is reasonable for prostatic PK/PD evaluation.

In the population PK modeling, we analyzed all concentration-time data by using hybrid modeling, which is able to parameterize physiological factors such as $Q_{prostate}$ and $V_{prostate}$ since conventional PK model analysis[25] is difficult to include their factors.

Hybrid models, sometimes used for modeling of tissue concentrations, would be useful for predicting drug concentrations in other organs. All concentration-time data were adequately described by the hybrid model (Table 3). Although the prostate parameters ($\theta KP_{prostate}$, $\theta Q_{prostate}$ and $\theta V_{prostate}$) were fixed, they all had interindividual variability ($\eta KP_{prostate}$, $\eta Q_{prostate}$ and $\eta V_{prostate}$) estimated by fitting the observed prostate concentrations to the predicted concentrations for individual subjects. As shown above in the hybrid model equations, the prostate concentrations ($X(prostate)/V_{prostate}$) and the plasma concentrations ($X(central)/V_{central}$) were simultaneously modeled to depend on each other. Therefore, goodness-of-fit of the predicted concentrations (PRED and IPRED) and their residual errors (CWRES) should be qualified by plots for prostate as well as plasma. The diagnostic scatter plots and prediction-corrected visual predictive check plots both confirmed the relatively good stability and prediction capability of the model (Figures 1, 2). The PK behavior was consistent with a two-compartment plasma model. Soto *et al*. previously reported a two-compartment model with a simultaneous fit of ampicillin and sulbactam.[26] Soto *et al*. reported mean values of CL = 10.7-10.4 (L/h), $V_{central}$ = 9.97-10.2 (L), Q = 4.14-4.58 (L/h), and $V_{peripheral}$ = 4.48-4.04 (L), similar to our

parameters. Therefore, the model and its parameter estimates were considered to be adequate, and to have good predictive performance for PK/PD evaluation use.

Using the developed model, PK/PD target attainment in plasma and prostate tissue for different dosing regimens were estimated. The results of the stochastic simulation indicated that the probabilities of attaining site-specific PK/PD targets in prostate tissue (Figure 3B) were lower than the probabilities in plasma (Figure 3A). Thus, PK/PD should be assessed in prostate tissue (the site of bacterial prostatitis and surgery) rather than in plasma. Assuming empirical treatment, 3 g ampicillin-sulbactam four times daily (12 g/day) achieved ≥90% expected probability of attaining the bactericidal target of 50% T > MIC (for therapeutic use, assuming that the host's immune status is poor) only against *E. faecalis* in patients with CL_{cr} = 30 mL/min (Table 5). Therefore, empirical treatment with ampicillin-sulbactam for prostatitis may be limited.

In case of the definitive treatment, the site-specific PK/PD breakpoints of 3 g ampicillin-sulbactam four times daily (12 g/day) were 0.5 μg/mL for CL_{cr} = 90 mL/min, 1 μg/mL (MIC_{50} of the *E. faecalis* isolates) for CL_{cr} = 60 mL/min, and 4 μg/mL (MIC_{50} of the *Klebsiella* species isolates) for CL_{cr} = 30 mL/min (Table 4). Thus, the

probabilities of attaining PK/PD target were lower as renal function increased. Accordingly, while the dosing regimens in patients with impaired renal function can be selected based on the site-specific PK/PD breakpoint, the regimen is almost limited to the maximum dose in patients with normal renal function.

In acute bacterial prostatitis, ampicillin in conjunction with gentamicin has been used for severely ill patients or those with urosepsis.[7] The recommended dose of ampicillin against *E. faecalis* indicates 2 g four times daily or 2 g six times daily.[6,7] However, an ampicillin dosing regimen for bacterial prostatitis based on prostatic PK/PD evaluation has not been recommended. The results of our stochastic PK/PD simulation study in prostate tissue indicated an even high dosing regimen (2 g-1 g ampicillin-sulbactam four times daily) did not achieve the site-specific PK/PD breakpoint of MIC = 1 μg/mL (MIC_{50} of the *E. faecalis* isolates) in typical patients with high renal function (CL_{cr} = 90 mL/min). Therefore, considering that MIC distribution of ampicillin against *E. faecalis* is mostly the same as ampicillin-sulbactam combination (MIC_{50} = 1 μg/mL),[23] higher dosing regimens (e.g. 2 g ampicillin six times daily) may be required. Since β-lactamase-producing strains of *E. faecalis* have been reported, a β-lactamase inhibitor can be expected to be useful in bacterial prostatitis with *E. faecalis*.[27-30]

Ampicillin-sulbactam has also been used for antibacterial prophylaxis in urological surgeries such as prostatectomy. Hence, we evaluated the probability of attaining the bacteriostatic target of 30% T > MIC (for prophylactic use, assuming that the host's immune status is good), in addition to the bactericidal target of 50% T > MIC (for therapeutic use, assuming that the host's immune status is poor). The regimen of 3 g ampicillin-sulbactam four times daily (12 g/day) achieved ≥90% expected probability of attaining the bacteriostatic target against *E. faecalis* and *Proteus* species in patients with CL_{cr} = 30 mL/min (Table 5). The site-specific PK/PD breakpoints of 3 g ampicillin-sulbactam four times daily (12 g/day) were 2 μg/mL (MIC_{50} of the *Proteus* species isolates) for CL_{cr} = 90 mL/min, 4 μg/mL (MIC_{50} of the *Klebsiella* species isolates) for CL_{cr} = 60 mL/min, and 8 μg/mL (MIC_{50} of the *E. coli* isolates) for CL_{cr} = 30 mL/min (Table 4). In patients with lower renal function (CL_{cr} = 30 mL/min), it is assumed that 3 g ampicillin-sulbactam four times daily (every 6 h) is capable of prostatic bacteriostatic activity against causative pathogens (*E. coli* in UTI). However, if the patients have normal renal function (CL_{cr} = 60 and 90 mL/min), preoperative prophylaxis targeting *E. coli* in prostatectomy may be insufficient using 3 g every 6 h, and a shorter time interval may be required. A redosing interval for ampicillin-sulbactam

of 2 h is the current recommendation for antimicrobial prophylaxis because the half-life with normal renal function is 0.8-1.3 h.[31,32] Our results regarding normal renal function are consistent with these reports.

Finally, this study has some limitation. The drug concentrations observed in the current study were measurements of prostate tissue homogenate, which represent apparent concentrations but not the genuine concentrations in prostate tissue. Earlier studies[33] also used measurement of prostate tissue homogenate as a practical method and provided useful information. However, the problems with using measurement of tissue homogenate were pointed out[34].

Besides, the subjects of this study were uninfected patients with prostatic hyperplasia. Since inflammation at the prostate due to prostatitis often increases vascular permeability in prostate, penetration of ampicillin and sulbactam may be affected in these patients. Thus, the results of PK/PD simulation for the tested regimens may be conservative, and even lower dosing regimens may be effective. Therefore, to establish the therapeutic appropriateness of the present results, clinical studies are required in

infected patients to investigate the relationship between the results of site-specific PK/PD simulation and clinical efficacy.

Conclusion

Ampicillin and sulbactam penetration into prostate tissue are mostly the same, with a prostate tissue/plasma ratio of around 0.37. Since the mean ampicillin/sulbactam ratio in the prostate tissue (1.0 to 2) was unaffected, antibacterial activity of ampicillin-sulbactam combination was maintained in prostate tissue. The population PK modeling adequately predicted prostate tissue concentrations in our patient population. By using the site-specific PK/PD approach based on this model, we provide a useful dosing regimen for bacterial prostatitis and preoperative prophylaxis in prostatectomy in consideration of pathogens and various degrees of renal function.

Conflict of interest

No conflicts of interest have been declared.

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Figure legends

Figure 1. Diagnostic scatter plots of the final model for ampicillin and sulbactam.

(A) Scatter plots of the observed concentrations (DV) of ampicillin and sulbactam (○, 219 plasma samples; ×, 109 prostate samples) *vs.* population predicted concentrations (PRED) and DV *vs.* individual predicted concentrations (IPRED) for the final model. Each straight line represents the concordance line (Y=X). (B) Scatter plots of conditional weighted residuals (CWRES) *vs.* PRED and CWRES *vs.* time for the final model.

Figure 2. Visual predictive check plots

Visual predictive check plots representing prediction-corrected (Pred Corr) concentration for ampicillin (A) and sulbactam (B) in plasma and prostate tissue vs. time (h). Each panel shows observed 10, 50, and 90th percentile points (red lines), and predicted 90% CIs for 10, 50, and 90th percentile points (blue and red areas).

Figure 3. Probabilities of attaining the bacteriostatic (30% T > MIC) and bactericidal (50% T > MIC) targets for ampicillin.

Probabilities of attaining the bacteriostatic targets in plasma (A) and prostate tissue (B), at specific MICs using twice-daily (b.i.d.), three-times-daily (t.i.d.), and four-times-daily (q.i.d.) regimens. The dotted lines represent 90% probability.

Table 1. Demographic parameters of the 44 male subjects.

	Ampicillin-sulbactam 1.5 g (n = 22)	**Ampicillin-sulbactam 3.0 g (n = 22)**
Age (years)	71.4 ± 6.1	73.2 ± 5.2
Body weight (kg)	62.1 ± 9.0	59.7 ± 10.2
Body mass index (kg/m^2)	23.0 ± 3.1	22.8 ± 3.2
Blood urea nitrogen (mg/dL), normal range of 8-20	15.9 ± 3.7	15.5 ± 4.6
Serum creatinine (mg/dL), normal range of	0.86 ± 0.25	0.86 ± 0.23

0.65-1.07		
Creatinine clearance (mL/min)	73.3 ± 21.3	68.9 ± 23.2
Total bilirubin (mg/dL), normal range of 0.4-1.5	0.70 ± 0.26	0.68 ± 0.20
Alanine aminotransferase (U/L), normal range of 13-30	26.4 ± 18.5	21.3 ± 7.0
Aspartate aminotransferase (U/L), normal range of 10-42	26.9 ± 12.9	21.2 ± 7.2

Mean ± SD

Table 2. Non-compartmental pharmacokinetic parameters of ampicillin and sulbactam after 0.5-h infusions.

Specimen and parameter	Value					
	Ampicillin 1 g (22 subjects)	Sulbactam 0.5 g (22 subjects)	Ampicillin/sulbactam ratio (1 g/0.5 g)	Ampicillin 2 g (22 subjects)	Sulbactam 1 g (22 subjects)	Ampicillin/sulbactam ratio (2 g/1 g)
Plasma						
C_{max} (μg/mL)	72.6 ± 18.9 (n = 22)	36.5 ± 10.1 (n = 22)	2.03 ± 0.44	155.0 ± 54.2 (n = 22)	62.9 ± 17.4 (n = 22)	2.42 ± 0.39
AUC (μg·h/mL)	102.6 ± 41.9 (n = 22)	56.6 ± 19.8 (n = 22)	1.81 ± 0.33	208.2 ± 87.1 (n = 22)	96.7 ± 35.6 (n = 22)	2.12 ± 0.37
Prostate tissue						
C_{max} (μg/g)	22.8 ± 8.4 (n = 21)	12.4 ± 4.2 (n = 21)	1.83 ± 0.28	44.2 ± 20.3 (n = 22)	20.9 ± 7.0 (n = 22)	2.01 ± 0.59
AUC	32.9 ±	21.7 ±	1.67 ± 0.24	65.3 ±	30.1 ±	2.24 ± 0.78

(μg·h/g)	11.5 (n = 20)	6.4 (n = 20)	39.3 (n = 21)	15 (n = 19)
Prostate tissue/plasma ratio				
C_{max}	0.33 ± 0.12	0.37 ± 0.16	0.29 ± 0.09	0.34 ± 0.09
AUC	0.43 ± 0.11	0.42 ± 0.06	0.35 ± 0.26	0.35 ± 0.18

Mean ± SD

C_{max}, observed maximum concentration; AUC, area under the drug concentration - time curve from 0 to infinity calculated based on the trapezoidal rule.

Table 3. Population pharmacokinetic parameters for ampicillin and sulbactam in the physiologically based model.

Parameter	Ampicillin			Sulbactam		
	Estimate	(RSE%)	95%CI	Estimate	(RSE%)	95%CI
Fix effects parameter						
CL (L/h) = θ_{CL} × (CL_{cr}/68.3[a])$^{\theta\ CLcr\ on\ CL}$						
θ_{CL}(L/h)	11.03	(5.1)	9.76 - 11.89	10.50	(5.0)	9.29 - 10.97
$\theta_{CLcr\ on\ CL}$	0.831	(14.1)	0.319 - 1.10	0.774	(18.6)	0.389 - 0.997
$V_{central}$ (L) = $\theta_{Vcentral}$	7.80	(5.9)	7.31 - 10.19	8.96	(9.6)	7.27 - 10.65
Q (L/h) = θ_{Q}	7.07	(14.3)	4.23 - 13.04	7.29	(21.4)	3.82 - 10.35
$V_{peripheral}$ (L) = $\theta_{Vperipheral}$	3.98	(12.3)	3.17 - 5.40	4.93	(13.4)	3.64 - 6.67
$KP_{prostate}$ = $\theta_{KPprostate}$	0.37 Fixed		None	0.37 Fixed		None
$Q_{prostate}$(L/h) = $\theta_{Qprostate}$	0.311 Fixed		None	0.311 Fixed		None
$V_{prostate}$(kg) = $\theta_{Vprostate}$	0.05 Fixed		None	0.05 Fixed		None

Interindividual variability (exponential error model)						
η_{CL}	0.0985	(26.1)	0.0532 - 0.144	0.0626	(26.8)	0.0346 - 0.103
$\eta_{Vcentral}$	0.160	(21.3)	0.113 - 0.281	0.147	(27.5)	0.0891 - 0.191
η_{Q}	0.588	(44.2)	0.105 - 1.57	0.399	(48.4)	0.0286 - 0.991
$\eta_{Vperipheral}$	0.298	(37.2)	0.0208 - 0.621	0.177	(37.9)	0.0455 - 0.309
$\eta_{KPprostate}$	0.147	(28.8)	0.0719 - 0.237	0.0807	(28.6)	0.0445 - 0.134
$\eta_{Qprostate}$	0.592	(60.6)	0.300 - 0.932	0.511	(20.4)	0.182 - 1.28
$\eta_{Vprostate}$	0.592	(15.7)	0.301 - 0.932	0.511	(57.9)	0.182 - 1.28
Residual variability (additive error model)						
ε	2.70	(26.2)	2.36 - 4.86	1.22	(38.8)	0.948 - 2.11

CI, confidence interval determined from 1000 bootstrap replicates RSE, relative standard error θ, population mean value; η, random variable which is normally distributed with a mean of zero and variance ε, random error which is normally distributed with a mean of zero and variance [a]Median as creatinine clearance in 44 subjects

Table 4. Pharmacokinetic/pharmacodynamic breakpoints for ampicillin in prostate tissue, using different ampicillin-sulbactam regimens.

Ampicillin-Sulbactam regimen (0.5-h infusion)	Bacteriostatic target (30% T > MIC)	Bactericidal target (50% T > MIC)
CL_{cr} = 90 mL/min		
1.5 g b.i.d (total 3 g/day)	-	-
3.0 g b.i.d (total 6 g/day)	0.25	-
1.5 g t.i.d (total 4.5 g/day)	0.5	-
3.0 g t.i.d (total 9 g/day)	1	-
1.5 g q.i.d (total 6 g/day)	1	0.25
3.0 g q.i.d (total 12 g/day)	2	0.5
CL_{cr} = 60 mL/min		
1.5 g b.i.d (total 3 g/day)	0.25	-
3.0 g b.i.d (total 6 g/day)	0.5	-
1.5 g t.i.d (total 4.5 g/day)	1	0.25
3.0 g t.i.d (total 9 g/day)	2	0.5
1.5 g q.i.d (total 6 g/day)	2	0.5

3.0 g q.i.d (total 12 g/day)	4	1
CL_{cr} = 30 mL/min		
1.5 g b.i.d (total 3 g/day)	2	0.5
3.0 g b.i.d (total 6 g/day)	4	1
1.5 g t.i.d (total 4.5 g/day)	4	1
3.0 g t.i.d (total 9 g/day)	8	2
1.5 g q.i.d (total 6 g/day)	4	2
3.0 g q.i.d (total 12 g/day)	8	4

Pharmacokinetic/pharmacodynamic breakpoints are defined as the highest MIC at which ≥90% of probabilities attaining the targets.

T > MIC for ampicillin in prostate tissue. Note: b.i.d., t.i.d. and q.i.d. indicate twice-daily, three-times-daily and four-times-daily, respectively.

Table 5. Expected probabilities of attaining bacteriostatic and bactericidal targets for ampicillin in prostate tissue, against bacterial populations using different ampicillin-sulbactam regimens.

Ampicillin-sulbactam regimen (0.5-h infusion)	%Expected probability of attaining bacteriostatic target (30% T > MIC) in prostate tissue					
	Escherichia coli	*Klebsiella* species	*Proteus* species	*Enterococcus faecalis*	*Enterococcus faecium*	*Pseudomonas aeruginosa*
CL_{cr} = 90 mL/min						
1.5 g b.i.d (total 3 g/day)	9.1	10.4	25.8	36.2	7.9	0.5
3.0 g b.i.d (total 6 g/day)	19.7	21.1	42.5	57.4	12.3	0.7
1.5 g t.i.d (total 4.5 g/day)	25.7	26.7	52.0	69.9	14.7	0.8
3.0 g t.i.d (total 9 g/day)	40.5	42.9	67.6	84.2	20.4	1.1
1.5 g q.i.d (total 6 g/day)	38.8	40.8	66.9	85.0	19.1	1.0
3.0 g q.i.d (total 12 g/day)	53.3	56.8	78.7	91.8	27.1	1.4

CL_{cr} = 60 mL/min						
1.5 g b.i.d (total 3 g/day)	21.4	22.4	46.4	63.2	13.1	0.7
3.0 g b.i.d (total 6 g/day)	35.9	37.9	62.7	79.7	18.4	1.0
1.5 g t.i.d (total 4.5 g/day)	39.6	41.6	67.9	86.1	19.4	1.0
3.0 g t.i.d (total 9 g/day)	54.1	57.6	79.3	92.3	27.3	1.5
1.5 g q.i.d (total 6 g/day)	50.5	54.3	77.5	92.2	23.9	1.3
3.0 g q.i.d (total 12 g/day)	64.7	67.5	85.7	94.3	36.8	2.4
CL_{cr} = 30 mL/min						
1.5 g b.i.d (total 3 g/day)	45.4	48.2	73.2	90.0	21.4	1.1
3.0 g b.i.d (total 6 g/day)	59.4	63.1	82.9	93.5	31.3	1.8
1.5 g t.i.d (total 4.5 g/day)	57.2	62.1	82.4	94.0	28.1	1.5
3.0 g t.i.d (total 9 g/day)	71.8	72.7	88.8	94.8	46.0	4.2
1.5 g q.i.d (total	64.6	68.6	86.3	94.6	35.1	2.0

6 g/day)						
3.0 g q.i.d (total 12 g/day)	79.7	77.4	91.5	95.2	59.6	9.4

Ampicillin-sulbactam regimen (0.5-h infusion)	%Expected probability of attaining bactericidal target (50% T > MIC) in prostate tissue					
	Escherichia coli	*Klebsiella* species	*Proteus* species	*Enterococcus faecalis*	*Enterococcus faecium*	*Pseudomonas aeruginosa*
CL_{cr} = 90 mL/min						
1.5 g b.i.d (total 3 g/day)	1.0	1.6	4.8	6.7	1.9	0.13
3.0 g b.i.d (total 6 g/day)	3.6	4.4	11.5	16.2	3.9	0.25
1.5 g t.i.d (total 4.5 g/day)	6.5	7.8	20.1	28.3	6.4	0.42
3.0 g t.i.d (total 9 g/day)	15.3	16.6	35.5	48.4	10.4	0.61
1.5 g q.i.d (total 6 g/day)	16.1	17.3	38.5	53.2	11.1	0.65
3.0 g q.i.d (total	29.6	31.2	55.6	72.5	16.1	0.88

12 g/day)						
CL_{cr} = 60 mL/min						
1.5 g b.i.d (total 3 g/day)	4.6	5.6	15.3	21.5	5.0	0.33
3.0 g b.i.d (total 6 g/day)	11.6	12.7	28.3	39.0	8.5	0.51
1.5 g t.i.d (total 4.5 g/day)	17.2	18.3	40.1	55.3	11.5	0.67
3.0 g t.i.d (total 9 g/day)	31.0	32.5	56.9	73.8	16.5	0.90
1.5 g q.i.d (total 6 g/day)	30.7	31.8	58.0	76.4	16.4	0.88
3.0 g q.i.d (total 12 g/day)	45.5	48.4	72.1	87.6	22.7	1.2
CL_{cr} = 30 mL/min						
1.5 g b.i.d (total 3 g/day)	23.7	24.7	49.1	66.2	13.9	0.77
3.0 g b.i.d (total 6 g/day)	38.1	40.4	64.6	81.0	19.3	1.0
1.5 g t.i.d (total 4.5 g/day)	42.4	44.7	70.3	87.7	20.5	1.1
3.0 g t.i.d (total 9 g/day)	56.7	60.2	80.9	92.7	29.6	1.7

1.5 g q.i.d (total 6 g/day)	52.9	56.9	79.1	92.9	25.5	1.3
3.0g q.i.d (total 12 g/day)	67.1	69.3	86.7	94.5	40.1	3.2

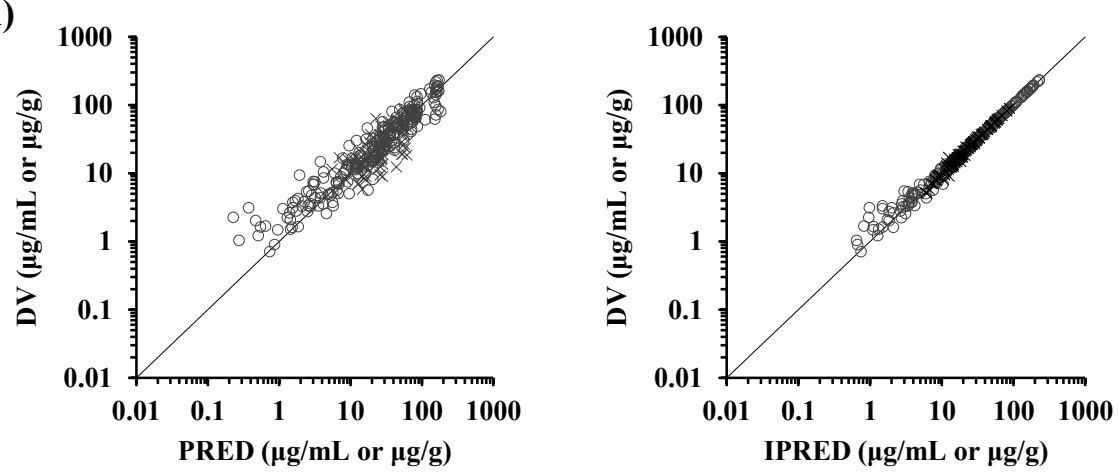
Note: b.i.d., t.i.d. and q.i.d. indicate twice-daily, three-times-daily and four-times-daily, respectively.

Figure 1. Diagnostic scatter plots of the final model for ampicillin and sulbactam

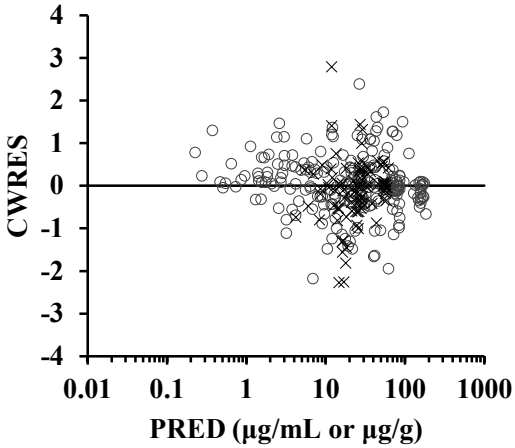
(A) Scatter plots of the observed concentrations (DV) of ampicillin and sulbactam (○, 219 plasma samples; ×, 109 prostate samples) *vs.* population predicted concentrations (PRED) and DV *vs.* individual predicted concentrations (IPRED) for the final model. Each straight line represents the concordance line (Y=X). (B) Scatter plots of conditional weighted residuals (CWRES) *vs.* PRED and CWRES *vs.* time for the final model.

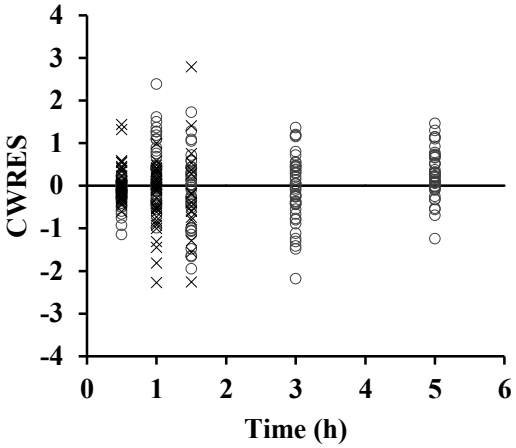
Ampicillin

(A)



(B)





Sulbactam

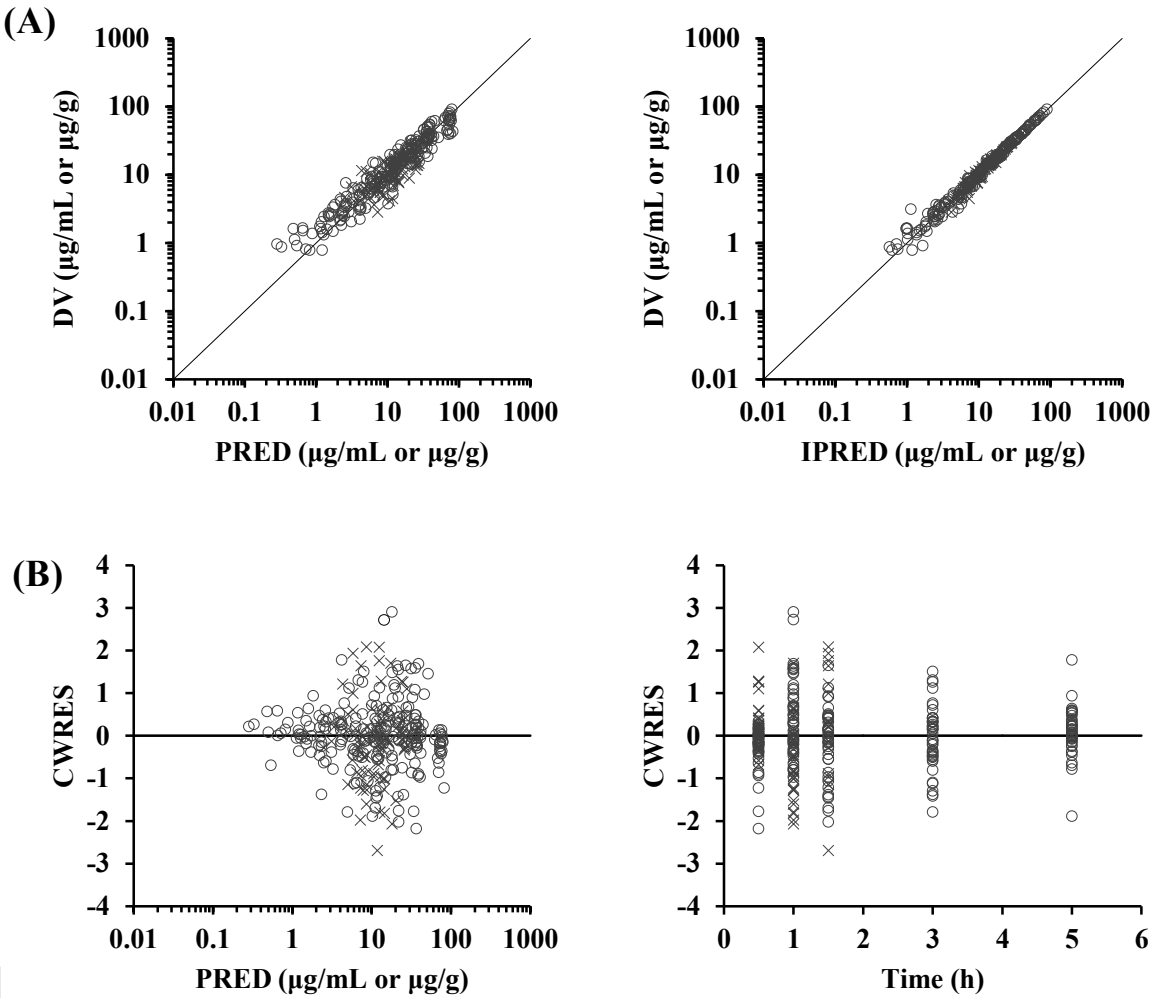
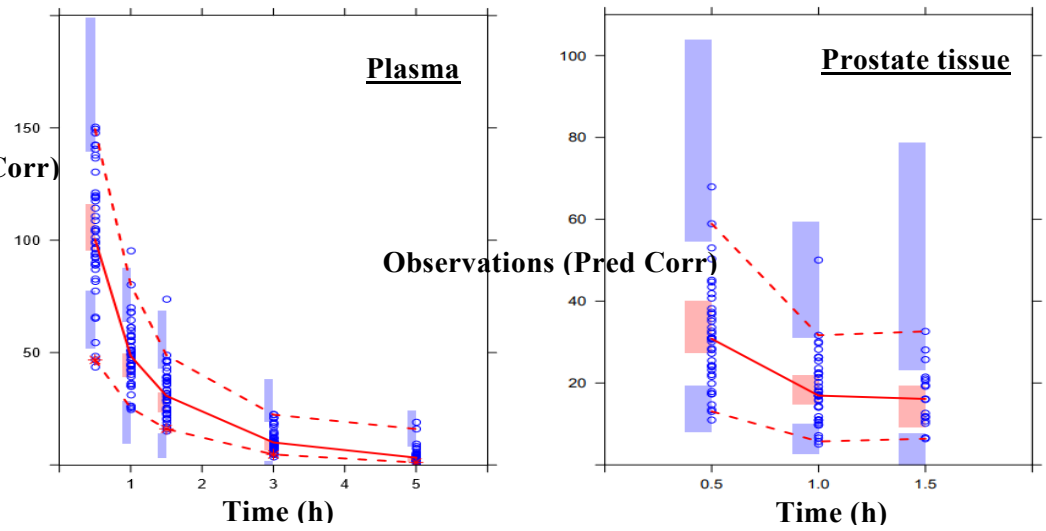


Figure 2. Visual predictive check plots

Visual predictive check plots representing prediction-corrected (Pred Corr) concentration for ampicillin (A) and sulbactam (B) in plasma and prostate tissue *vs.* time (h). Each panel shows observed 10, 50, and 90th percentile points (red lines), and predicted 90% CIs for 10, 50, and 90th percentile points (blue and red areas).

(A) Ampicillin



(B) Sulbactam

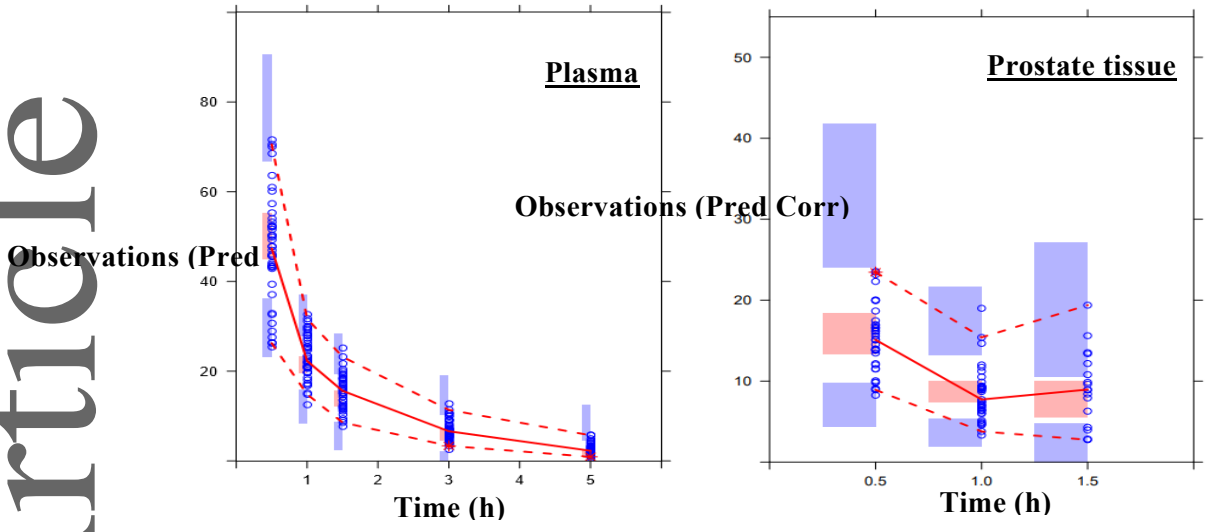
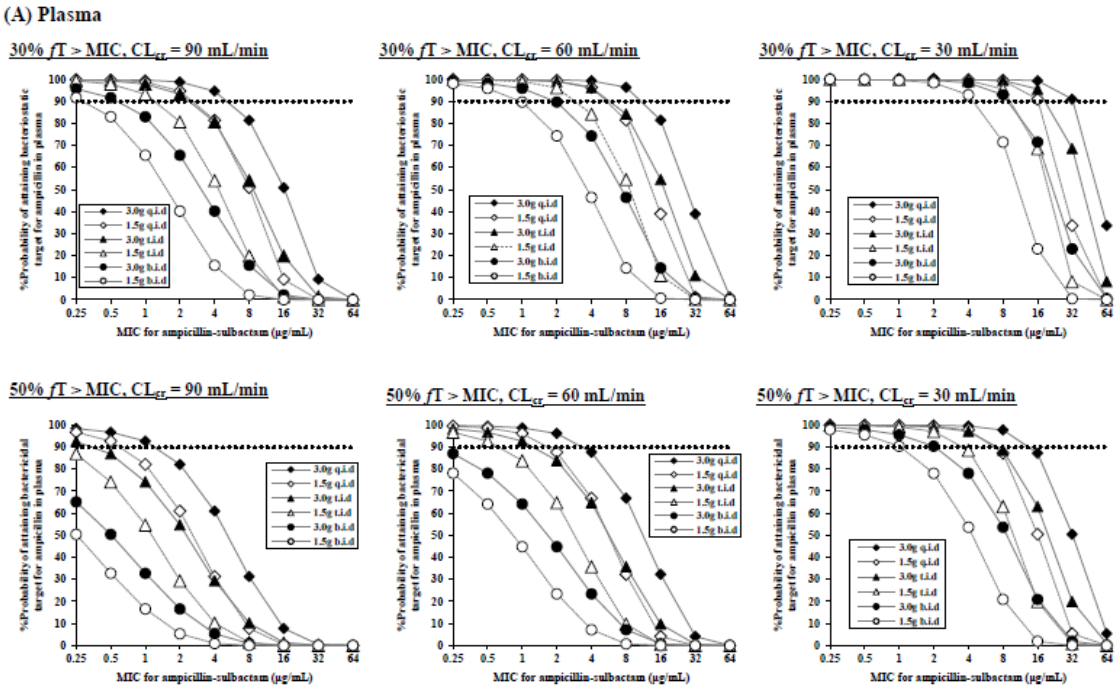


Figure 3. Probabilities of attaining the bacteriostatic (30% T > MIC) and bactericidal (50% T > MIC) targets for ampicillin, in plasma (A) and prostate tissue (B), at specific MICs using twice-daily (b.i.d.), three-times-daily (t.i.d.) and four-times-daily (q.i.d.) regimens. The dotted lines represent 90% probability.



(B) Prostate tissue