Identification of a pharmacokinetic interaction between teicoplanin and sulfo-butyl ether-β-cyclodextrin, an excipient in the intravenous posaconazole formulation

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Abstract

Background

Patients undergoing hematopoietic stem cell transplantation (HSCT) often receive multiple antibiotics and antifungal agents concurrently, making it crucial to understand potential pharmacokinetic interactions. We report here an interaction between the glycopeptide antibiotic teicoplanin (TEIC) and sulfo-butyl ether-β-cyclodextrin (SBECD), a solubilizing excipient in the intravenous formulation of posaconazole (PSCZ).

Methods

We performed a single-center retrospective analysis of HSCT patients who received oral and intravenous PSCZ during TEIC therapy. Associations between PSCZ administration and TEIC concentration-to-dose (C/D) ratios were evaluated using linear mixed-effects models. In rats, we examined the effects of intravenous PSCZ and SBECD on TEIC pharmacokinetics by assessing the area under the concentration–time curve (AUC) and urinary excretion of total TEIC and its components. Molecular docking and in vitro protein-binding assays were also conducted to investigate the interaction between TEIC and SBECD.

Results

In HSCT patients, TEIC C/D ratios were significantly lower during intravenous PSCZ administration but not during oral PSCZ use. In rats, both intravenous PSCZ and SBECD decreased TEIC AUC and increased urinary excretion, particularly for the A2 group. Docking simulations indicated that the hydrophobic side chain of TEIC A2-2 fit within the SBECD cavity, and in vitro assays confirmed SBECD concentration-dependent increases in TEIC unbound fractions.

Conclusion

Co-administration of intravenous PSCZ containing SBECD may reduce TEIC protein binding, thereby enhancing renal elimination.

Introduction

Patients who undergo hematopoietic stem cell transplantation (HSCT) are susceptible to bacterial and fungal infections due to immunosuppression caused by conditioning chemotherapy before transplantation and immunosuppressive therapy afterward. Consequently, multiple antibiotics and antifungal agents are often administered concomitantly in HSCT patients for both prophylaxis and treatment of infections. Teicoplanin (TEIC), a glycopeptide antibiotic, is one of the agents frequently used in this population. Along with vancomycin, TEIC is widely employed in the treatment of methicillin-resistant *Staphylococcus aureus* infections, and it is also administered empirically when gram-positive bacterial infection is suspected. TEIC undergoes minimal metabolism and is primarily eliminated via the kidneys. Compared with vancomycin, TEIC exhibits a higher protein binding rate, a larger volume of distribution, and a substantially longer half-life of approximately 83 to 168 hours (1, 2). Target trough concentrations required for therapeutic efficacy have been established based on pharmacokinetic-pharmacodynamic analyses (3, 4). Thus, maintaining appropriate plasma concentrations is critical for successful treatment, and fluctuations in TEIC exposure may result in treatment failure, highlighting the need to fully elucidate both inter- and intra-individual factors contributing to its pharmacokinetic variability.

Additionally, azole antifungal agents are commonly administered to HSCT patients for the prevention of fungal infections. Posaconazole (PSCZ), an azole antifungal agent, is known not only for its potent antifungal activity but also for its inhibition of the drug-metabolizing enzyme CYP3A and the efflux transporter P-glycoprotein in the liver and small intestine (5, 6). Therefore, co-administration of PSCZ with drugs that are substrates of these enzymes or transporter may reduce the clearance of the co-administered drugs, potentially leading to drug–drug interactions. In contrast, for renally excreted drugs, PSCZ is theoretically unlikely to exert a significant effect on their pharmacokinetics.

However, we report here that the plasma concentration of TEIC significantly decreased when the intravenous formulation of PSCZ was co-administered in HSCT patients. In this study, we also assessed the reproducibility of this phenomenon using an animal model. Furthermore, we identified sulfo-butyl ether-β-cyclodextrin (SBECD), a pharmaceutical excipient contained in the intravenous PSCZ formulation, as a potential

contributor to the reduction in plasma teicoplanin concentrations. We also predicted the formation of an inclusion complex of SBECD with TEIC and evaluated the effect of SBECD on the protein binding of TEIC.

Material and Methods

Evaluation of the effects of oral and intravenous administration of PSCZ on plasma concentrations of TEIC in HSCT patients

We conducted a single-center retrospective analysis of patients who underwent HSCT and received the tablet formulation of PSCZ (oral PSCZ) and the injectable formulation of PSCZ (i.v. PSCZ) during TEIC treatment between April 2020 and January 2022 at the Department of Hematology, Kyoto University Hospital. Eligible patients were required to have plasma TEIC concentration data available under three conditions: without PSCZ, with oral PSCZ, and with i.v. PSCZ. This study was conducted in accordance with the Declaration of Helsinki and its amendments, and was approved by the Ethics Committee of the Kyoto University Graduate School and Kyoto University Hospital (Approval No. R2470).

We extracted all available data on trough plasma concentrations of TEIC from the hospital's electronic medical database. Plasma concentrations of TEIC were measured in the hospital's central laboratory by latex immunoturbidimetry using the Cobas 6000 system. TEIC plasma concentration data were included if they met the following criteria: (i) obtained at least three days after maintaining a constant dosage following TEIC loading, (ii) obtained at least three days after a dosage adjustment, or (iii) obtained at least three days after switching the formulation of PSCZ. As additional variables, we collected sex and age, which are generally assumed to influence drug pharmacokinetics, as well as serum albumin levels and estimated glomerular filtration rate (eGFR), which are known to affect the pharmacokinetics of TEIC (7).

To evaluate an association between the PSCZ administration and the change in pharmacokinetics of TEIC, the effects of PSCZ on the concentration-to-dose (C/D) ratio of TEIC were estimated using linear mixed-effects models:

$$C/D\ ratio\ = \alpha + \beta_1 * I_{oral} + \beta_2 * I_{intravenous} + \gamma + \varepsilon$$

where α is the estimate of intercept, β is the estimate of fixed effect, I_{oral} and $I_{\text{intravenous}}$ are the indicator variable, γ is the estimate of random effect for the intercept

(individual-level residual with mean zero and variance σ^2_γ), and ε is the estimated residual error (with mean zero and variance σ^2_ε). I_{oral} = 1 if oral PSCZ was co-administered and 0 otherwise; $I_{intravenous}$ = 1 if i.v. PSCZ was co-administered and 0 otherwise. The effects of PSCZ were further adjusted for age, sex, serum albumin, and eGFR, which were incorporated as independent covariates with fixed effects. Analyses were carried out using the JMP software version 18 (SAS Institute Inc., Cary, NC, U.S.A.)

Evaluation of the Pharmacokinetics of Teicoplanin in Rats

Eight-week-old male Wistar/ST rats were purchased from SLC Animal Research Laboratories (Shizuoka, Japan) and maintained according to the guidelines for Animal Experiments of Kyoto University, Kyoto, Japan. The study design was approved by the Animal Research Committee of the Graduate School of Medicine, Kyoto University, Kyoto, Japan (permit numbers: Medkyo 22119 and 23107). The rats were housed in a specific pathogen-free facility, maintained in a temperature-controlled environment with a 12-h light/dark cycle, and fed a standard diet and water ad libitum. For the administration of TEIC and PSCZ to rats, the commercially available intravenous formulations, Teicoplanin for Intravenous Infusion 200 mg (Towa) (Towa Pharmaceutical Co., Ltd. Osaka, Japan) and Noxafil® for Intravenous Infusion 300 mg (MSD K.K., Tokyo, Japan) were used., SBECD was purchased from (ChemScene, NJ, USA). All other reagents and solvents used were of analytical or LC–MS grade.

Rats were anesthetized with a combination of medetomidine, midazolam, and butorphanol, and catheters were inserted into the left femoral vein and right femoral artery using polyethylene tubing (SP-31; Natsume Seisakusho, Tokyo, Japan). Saline, PSCZ (40 mg/kg PSCZ with 890.67 mg/kg SBECD), or SBECD alone (890.67 mg/kg) was administered through the femoral vein. These doses were set with reference to the human equivalent dose in rats, where the dose per body weight is approximately six times the dose for humans (8).Thirty minutes later, TEIC (20 mg/kg) was injected via the femoral vein. Six rats per group were included in the experiments. PSCZ is highly hydrophobic, making it difficult to dissolve in a solvent suitable for intravenous administration without the use of SBECD. Therefore, a PSCZ-alone group was not included in the study. Blood samples were collected from the femoral artery at the end

of TEIC administration and at 5, 15, 30, 60, 90, and 120 minutes thereafter. Plasma was separated by centrifugation. Urine was collected from the bladder via a polyethylene tube for 120 minutes after TEIC administration. Plasma and urine samples were deproteinized by adding four volumes of methanol, followed by centrifugation at 10,000 × g for 5 minutes. A 50 μL aliquot of the supernatant was mixed with 200 μL of methanol. Urine samples were further diluted fivefold with methanol. Finally, all samples were filtered through a 0.45 μm membrane filter prior to analysis.

Quantification of TEIC was performed using a triple quadrupole MS/MS system (LCMS-8040; Shimadzu, Japan) equipped with an electrospray ionization source. The mobile phases were 0.1% formic acid in water (phase A) and 0.1% formic acid in acetonitrile (phase B). The gradient elution program was as follows: 0–1.0 min, 5% B; 1.0–3.0 min, 5–100% B; 3.0–3.5 min, 100% B; 3.5–4.0 min, 100–5% B; 4.0–6.5 min, 5% B. The flow rate was 0.25 mL/min, the column oven temperature was 60 °C, and the injection volume was 5 μL. Chromatographic separation was achieved using an ACQUITY UPLC BEH C18 column (50 × 2.1 mm, 1.7 μm particle size; Waters, USA). Detection was performed in the positive ion mode using multiple reaction monitoring. Since the clinically used intravenous formulation of TEIC comprises five major components (A_{2-1}, A_{2-2}, A_{2-3}, A_{2-4}, and A_{2-5}), and one hydrolysis component (A_{3-1}) (Figure 1), the following ion transitions were monitored to detect each component: A_{2-1}, from *m/z* 939.7 to 314.2; A_{2-2} and A_{2-3}, from *m/z* 940.7 to 316.2; A_{2-4} and A_{2-5}, from *m/z* 947.8 to 330.2; A_{3-1}, from *m/z* 782.4 to 203.7 (9).

The area under the plasma concentration–time curve (AUC) and urinary excretion of TEIC were determined over 120 minutes after administration. The AUC and urinary excretion were for total TEIC, and also for each individual component were evaluated. Statistical analysis was performed using the GraphPad Prism version 8.0 software (GraphPad, San Diego, CA, USA). The data were analyzed using one-way analysis of variance (ANOVA); a P-value < 0.05 was considered-statistically significant.

Molecular docking simulation

Since TEIC A_{2-2} is the major component of the clinical formulation and its conformation is crystallographically characterized, only this dominant analogue was considered for molecular modeling. The 3D structure for TEIC A_{2-2} was obtained from

Protein Data Bank (PDB) (ID: 4PJZ) (10). The structure of SBECD was constructed using Avogadro software (ver. 1.2.0) (11) on the basis of the 3D structures of native β-CD that was retrieved from the PDB (ID: 3CGT). Based on previous reports (12), the structure of SBECD was prepared by assuming that seven glucopyranose units were substituted with sulfobutyl ether, namely four in position C2 on the secondary face (residues 1, 3, 5 and 7) and three in position C6 on the primary face (residues 2, 4 and 6), in accordance with the average degrees of substitution of SBECD reagent (6.0-7.1). The molecular geometry of TEIC A_{2-2} and SBECD were fed into GAMESS (ver. 2023 R1) (13) for geometry optimization using the semiempirical quantum chemistry method PM3. Treating the geometry optimized structures of TEIC A_{2-2} and SBECD as a ligand and receptor, respectively, molecular docking to obtain complexes of TEIC A_{2-2} with SBECD was then performed with 100 runs using the Lamarckian genetic algorithm in AutoDock 4.2 (14). The receptor and ligand were assigned Gasteiger partial charges and the rotatable bonds were not defined. All the other parameters were the default values of AutoDock 4.2.

Evaluation of the effect of SBECD on the protein binding of TEIC in human serum

SBECD (40 mg/mL in distilled water) was diluted with human serum (Kojin Bio, Saitama, Japan) to prepare serum samples containing 0, 100, 300, and 1000 μg/mL of SBECD. These concentrations are within the range observed in clinical settings (15, 16). Aliquots of 380 μL of each serum sample were incubated at 37 °C for 30 minutes. Subsequently, 20 μL of TEIC injection solution, prepared with distilled water to a concentration of 0.8 mg/mL, was added to achieve a final concentration of 40 μg/mL. This corresponds to the upper limit of the clinically targeted trough concentration for TEIC. The samples were then incubated at 37 °C for 60 minutes, with gentle mixing for 10 seconds every 10 minutes during incubation. After incubation, 300 μL of each sample was immediately collected and filtered through an ultrafiltration membrane (30 kDa, Millipore, Tokyo, Japan). Calibration curves for TEIC were generated using serum subjected to the same ultrafiltration procedure as the matrix. The concentration of TEIC in the filtrate was quantified using the method described above, and the unbound fraction was calculated relative to the concentration of 40 μg/mL. Data were analyzed using one-way analysis of variance (ANOVA), and a P-value < 0.05 was considered

statistically significant.

Results

Decreased TEIC plasma concentrations following intravenous PSCZ administration in HSCT patients

This study included eight patients who underwent HSCT and received both TEIC and PSCZ during the observation period. TEIC plasma concentrations were measured under three conditions: without PSCZ, during oral PSCZ administration, and during intravenous PSCZ administration. Among these patients, TEIC was administered prior to PSCZ in five, while PSCZ was administered prior to TEIC in three. A total of 83 plasma concentration measurements were obtained: 23 without PSCZ, 27 during oral administration, and 33 during intravenous administration. The data points per person ranged from a minimum of 5 to a maximum of 18. Patient characteristics are summarized in Table 1. The average TEIC C/D ratio was 3.53 (standard deviation [SD], 1.29) in the absence of PSCZ, 3.10 (SD, 1.26) during oral PSCZ administration, and 2.23 (SD, 0.95) during intravenous administration (Figure 2). A linear mixed-effects model demonstrated that the C/D ratio was significantly lower during intravenous PSCZ administration compared with non-administration (estimate: -1.24; 95% confidence interval [CI], -1.74 to -0.74). After adjusting for serum albumin, eGFR, age, and sex as covariates, the reduction in the C/D ratio associated with intravenous PSCZ remained significant (estimate: -1.22; 95% CI, -1.84 to -0.60). This corresponds to an approximately 35% decrease compared with the non-PSCZ condition. In contrast, the effect of oral PSCZ administration on the TEIC C/D ratio relative to non-administration was not statistically significant (unadjusted: -0.36; 95% CI, -0.92 to 0.20; adjusted: -0.21; 95% CI, -0.88 to 0.45).

Changes in TEIC pharmacokinetics following SBECD administration in rats

The above results suggest that the intravenous formulation of PSCZ is specifically associated with reduced plasma concentrations of TEIC. Since the dosage of PSCZ was identical regardless of the route of administration (300 mg/day), we focused on SBECD, which is contained only in the intravenous formulation, as a potential factor influencing TEIC pharmacokinetics. To test this hypothesis, rats were pretreated with either the intravenous PSCZ formulation or SBECD, followed by TEIC administration, and the AUC and urinary excretion of TEIC were evaluated (Figure 3). Compared with

rats pretreated with saline, those pretreated with either intravenous PSCZ or SBECD showed a significant decrease in TEIC AUC and a significant increase in urinary excretion (Figure 3A–C). There were no significant differences between groups in plasma concentrations immediately after administration (Figure 3A), and urine volume (Figure 3D). Furthermore, the relative abundances of individual components of the TEIC formulation, A_{2-1}, $A_{2-2/2-3}$, $A_{2-4/2-5}$, and A_{3-1}, were determined. Following administration of intravenous PSCZ or SBECD, the AUC of the A_2 group significantly decreased, while its urinary excretion significantly increased (Figure 2E–G, 2I–K). In contrast, no significant effect was observed for A_{3-1} (Figure 2H, 2L).

Molecular modeling of TEIC A_{2-2} inclusion complex with SBECD

These findings indicate that SBECD contributes to the reduction of teicoplanin plasma concentrations, with a greater impact on the A_2 group compared to the A_{3-1}. Structural differences exist between these groups, as only the A_2 group possesses a long carbon chain (Figure 1). Furthermore, a previous study showed that a β□cyclodextrin derivative, 2-hydroxypropyl□β□cyclodextrin potentially prevents the hydrolysis of glycosyl group with a hydrophobic side chain of dalbavancin, a semisynthetic glycopeptide with an analogous molecular scaffold of TEIC (17). Therefore, we hypothesize that SBECD accommodates the side chain of TEIC, thereby inhibiting its binding to the serum proteins. To test this, we performed docking simulations for TEIC A_{2-2}, a major analogue of the TEIC, against SBECD by using AutoDock software. Through 100 docking runs, we obtained two probable binding modes of the complex of TEIC A_{2-2} with SBECD: the dimethyl terminus of TEIC A_{2-2} side chain is directed toward the primary face of the SBECD molecule for Type I (Figure 4A); and the dimethyl terminus is directed towards the secondary face of the SBECD molecule for Type II (Figure 4B). Regardless of the binding mode, most of the hydrophobic side chain of TEIC A_{2-2}, which contribute to an increased protein binding rates, was accommodated within the hydrophobic inner cavity of SBECD.

Effect of SBECD on the protein binding of TEIC

These findings suggest that SBECD exerts a strong influence on the protein binding of TEIC, particularly on the A_2 group. Therefore, we evaluated the unbound

fraction of TEIC in human serum containing clinically relevant concentrations of SBECD (Figure 5). The results demonstrated that the unbound fractions of both the A_2 group and $A_{3\text{-}1}$ increased in a concentration-dependent manner with increasing SBECD concentrations. Compared with the condition without SBECD, the unbound fractions of $A_{2\text{-}1}$, $A_{2\text{-}2/2\text{-}3}$, $A_{2\text{-}4/2\text{-}5}$, and $A_{3\text{-}1}$ increased by 3.4-fold, 9.6-fold, 25.9-fold, and 1.3-fold, respectively, at an SBECD concentration of 300 μg/mL.

Discussion

In HSCT patients, multiple antibiotics and antifungal agents are often used concurrently, making it essential to fully understand the potential interactions among these drugs. In this study, we demonstrated for the first time that co-administration of the intravenous formulation of PSCZ with TEIC in HSCT patients results in reduced TEIC plasma concentrations. A key strength of this study is that the reproducibility of this phenomenon was confirmed by integrating clinical observations with an animal model. Moreover, by focusing on the pharmaceutical excipient SBECD, we further elucidated its impact on TEIC protein binding in *in vitro* assays and the mode of inclusion complex formation through molecular modeling.

SBECD is a derivative of β-cyclodextrin, composed of seven glucose units linked in a ring, with a hydrophobic inner cavity and a hydrophilic outer surface. This structure enables it to encapsulate hydrophobic drugs, thereby improving their aqueous solubility (18-20). Notably, each vial of the intravenous PSCZ formulation (Noxafil® 300 mg) contains as much as 6,680 mg of SBECD. In general, cyclodextrin–drug inclusion complexes are thought to have minimal effects on pharmacokinetics, as they dissociate rapidly after intravenous administration (21-27). However, exceptionally stable complexes are known to markedly alter drug elimination pathways. For instance, the rocuronium–sugammadex complex exhibits a high stability constant, while rocuronium alone is excreted via bile, in the presence of sugammadex it is rapidly eliminated in urine (21). Similarly, drugs with an adamantane structure show particularly high affinity due to their close fit with the cyclodextrin cavity (28), and in fact, urinary excretion rates have been reported to increase from 0.1% to 37% in the presence of SBECD (29). In the present study, rats administered either the intravenous PSCZ formulation or SBECD alone exhibited a significant increase in TEIC urinary excretion, supporting the occurrence of an interaction between TEIC and SBECD in vivo.

Semisynthetic lipoglycopeptides, such as the TEIC A_2 group, telavancin, dalbavancin, and oritavancin, exhibit high protein binding and consequently much longer half-lives than vancomycin, owing to their lipophilic side chains (30). Although the binding affinity of TEIC to human serum albumin (HSA), the predominant serum protein, has been reported (31), its binding conformation remains unclear. Dalbavancin,

which shares large structural similarity with TEIC, binds to HSA by inserting its hydrocarbon chain into the hydrophobic pocket within subdomain IA of HSA, composed entirely of nonpolar amino acids (32). Given that TEIC, despite isoform differences, also possesses a long hydrocarbon chain and a conserved cyclic peptide core, it is likely to bind albumin in a similar manner. This hypothesis is consistent with our in vitro findings showing that A_{3-1} displays a higher proportion of the unbound fraction compared to the A_2 group. Furthermore, 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) has been shown to slow hydrolysis of the glycosidic linkage between the mannosyl aglycone and hydrophobic side chain of dalbavancin (17), suggesting that HP-β-CD interacts with and shields this region. The use of HP-β-CD as a pharmaceutical excipient to enhance the solubility of telavancin (Vibativ®) (33) and oritavancin (Kimyrsa®) (34) further supports our findings regarding TEIC–CD interactions. A_{2-2}, A_{2-3}, A_{2-4}, and A_{2-5} are the major components of clinical TEIC formulations. In this study, we further demonstrated that SBECD significantly increases the unbound fraction of TEIC, particularly within the A_2 group. These results suggest that the hydrophobic cavity of SBECD accommodates much of the hydrophobic side chain of TEIC A_2, thereby reducing protein binding and leading to decreased plasma concentrations through enhanced renal excretion.

In HSCT patients, the C/D ratio of TEIC decreased by an average of 1.2 when the intravenous formulation of PSCZ was administered, compared with no administration. This means that, when TEIC was administered at 10 mg/kg/day, co-administration of intravenous PSCZ would result in an approximate 12 μg/mL reduction in trough levels of TEIC. However, the clinical sample size in this study was limited, and large-scale prospective studies are needed to more accurately evaluate the magnitude of this effect. In addition, assessment of how these plasma concentration changes impact the efficacy of TEIC should be conducted through pharmacokinetics–pharmacodynamics analyses. Finally, since SBECD is widely used in injectable formulations beyond PSCZ, future studies should also investigate potential interactions between TEIC and other SBECD-containing formulations, as well as with drugs possessing similarly hydrophobic side chains.

Taken together, our findings suggest that co-administration of intravenous PSCZ containing SBECD with TEIC may reduce the protein binding of TEIC, thereby

promoting its renal excretion. The findings of this study provide a new perspective for assessing the risk of drug–drug interactions when using SBECD-containing formulations.

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Figure legends

Figure 1. Chemical structures of teicoplanin (TEIC, left) and sulfo-butyl ether-β-cyclodextrin (SBECD, right).

Figure 2. Trough plasma concentrations of TEIC in HSCT patients during periods without PSCZ, during oral administration, and during intravenous administration. The TEIC concentration/dose (C/D) ratios were obtained from 83 plasma concentration measurements across eight patients: 23 without PSCZ, 27 during oral administration, and 33 during intravenous (i.v.) administration. Bars indicate the mean C/D ratio, and error bars represent standard deviations.

Figure 3. Pharmacokinetics of TEIC in rats. Male Wistar/ST rats (8 weeks old) received an intravenous injection via the femoral vein of saline (Control), the PSCZ intravenous formulation (PSCZ), or SBECD alone (SBECD). Thirty minutes later, TEIC was administered intravenously. (A–D) The area under the plasma concentration–time curve (AUC) and urinary excretion of TEIC were evaluated over 120 minutes after TEIC administration. (E–L) The AUC and urinary excretion of individual TEIC components were also evaluated and expressed as relative values to the Control group. *$P < 0.05$, **$P < 0.01$, significantly different from the Control group (n = 6 per group).

Figure 4. Estimated binding modes of TEIC A_{2-2} with SBECD. The lowest TEIC A_{2-2} binding energy conformations for SBECD in the most probable docking clusters through 100 runs. The dimethyl terminus of TEIC A_{2-2} side chain is directed toward the primary face of the SBECD molecule in Type I (A) and is directed towards the secondary face of the SBECD molecule in Type II (B). The left, middle and right panels show the front, side and back views as chemical structure of TEIC in figure 1, respectively.

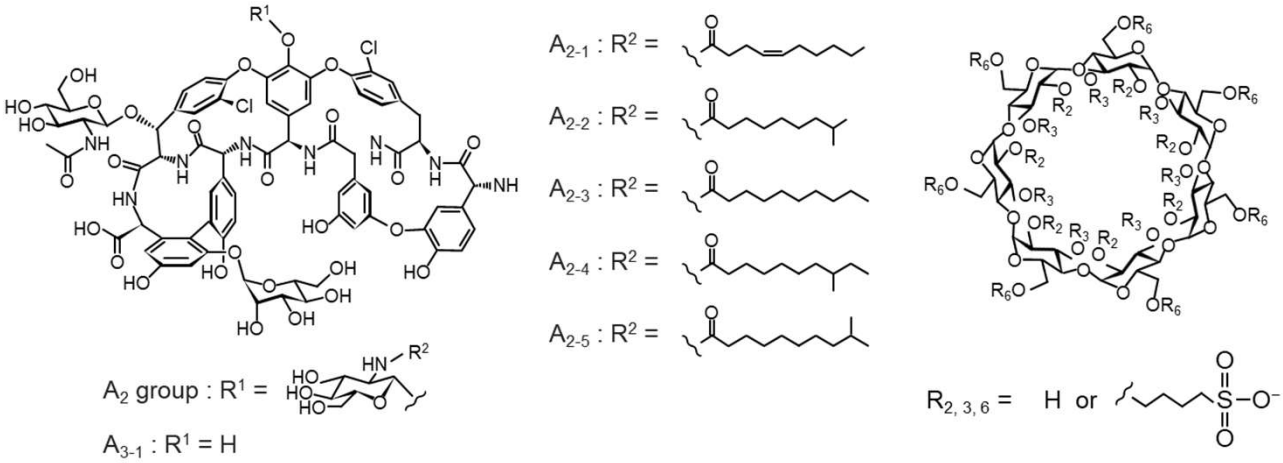
Figure 5. Unbound fraction of TEIC in human serum. Human serum containing various concentrations of SBECD was supplemented with TEIC. The unbound fraction of each TEIC component was determined. *$P < 0.05$, **$P < 0.01$, significantly different from the group without SBECD (“0”) (n = 3 per group).

Table 1. Characteristics of patients treated with teicoplanin and posaconazole/

Dose of teicoplanin, mg/kg/day (mean ± S.D.)	9.95 ± 3.64
Male/female, n	4/4
Age, years (mean ± S.D.)	45.9 ± 11.0
Serum albumin, g/dL (mean ± S.D.)	2.92 ± 0.45
estimated glomerular filtration rate, mL/min/1.73 m^2 (mean ± S.D.)	101.5 ± 46.3
Number of data points, n	
Without posaconazole	23
With oral posaconazole	27
With intravenous posaconazole	33

S.D., standard deviation. Posaconazole was administered at a dose of 300 mg per day, regardless of body weight or route of administration.

Figure 1



Teicoplanin (TEIC)

Sulfo-butyl ether-β-cyclodextrin (SBECD)

Figure 2

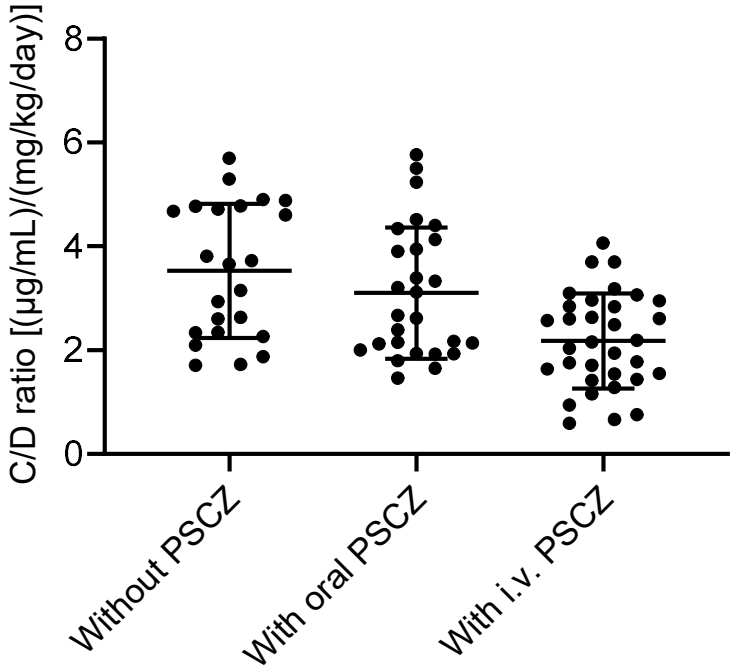

C/D ratio [(μg/mL)/(mg/kg/day)]
8
6
4
2
0
Without PSCZ
With oral PSCZ
With i.v. PSCZ

Figure 3

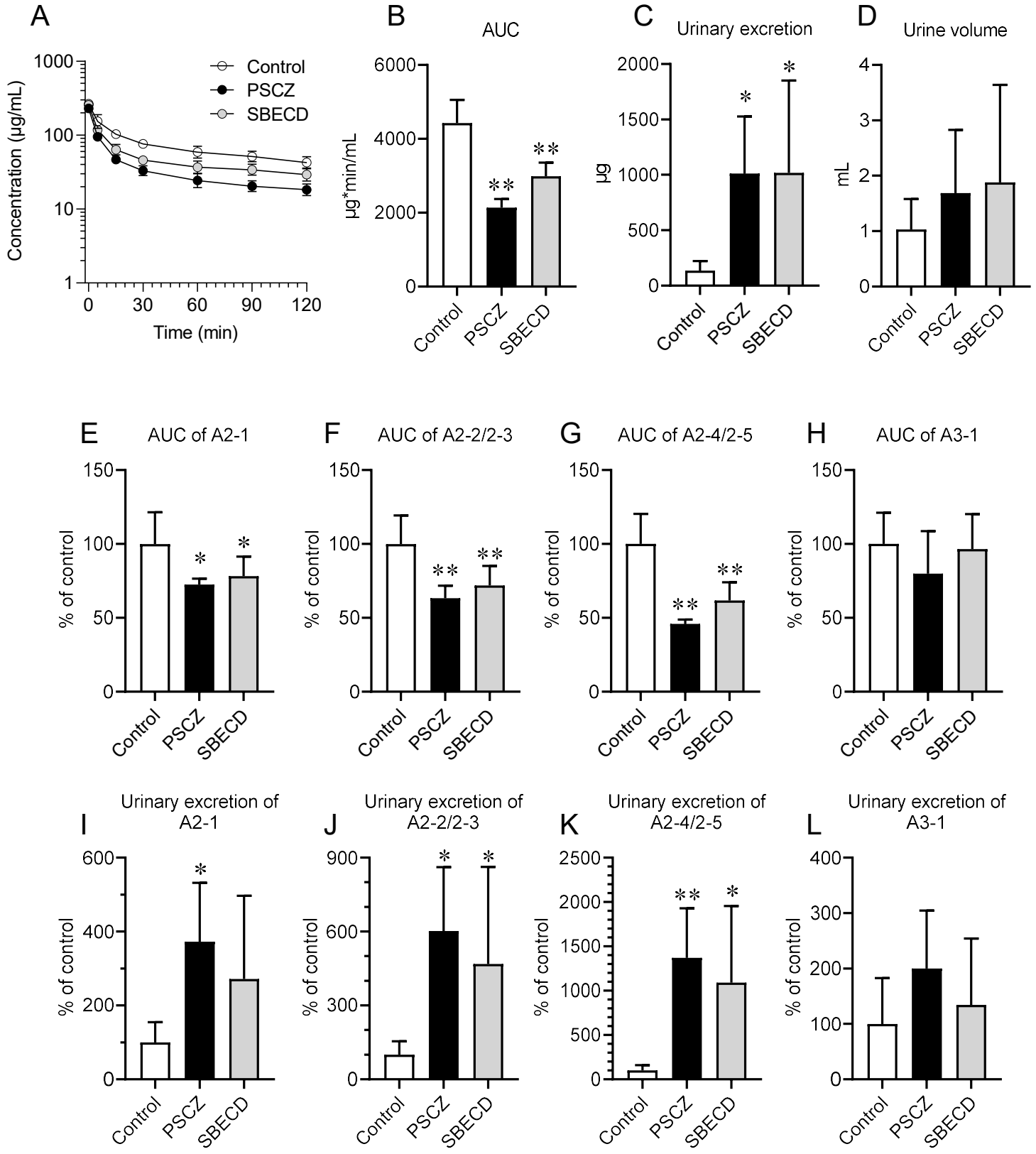

A
Control
PSCZ
SBECD
Concentration (μg/mL)
Time (min)
B
AUC
μg*min/mL
C
Urinary excretion
μg
D
Urine volume
mL
E
AUC of A2-1
F
AUC of A2-2/2-3
G
AUC of A2-4/2-5
H
AUC of A3-1
% of control
I
Urinary excretion of A2-1
J
Urinary excretion of A2-2/2-3
K
Urinary excretion of A2-4/2-5
L
Urinary excretion of A3-1

Figure 4

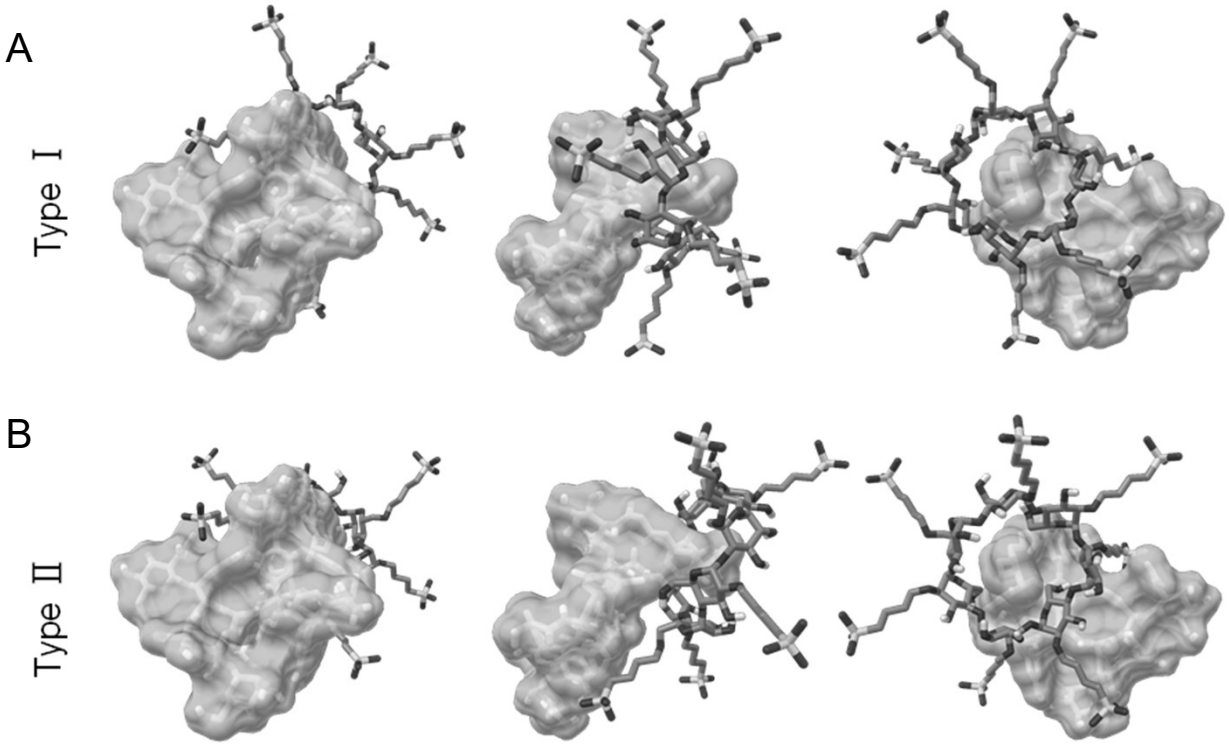
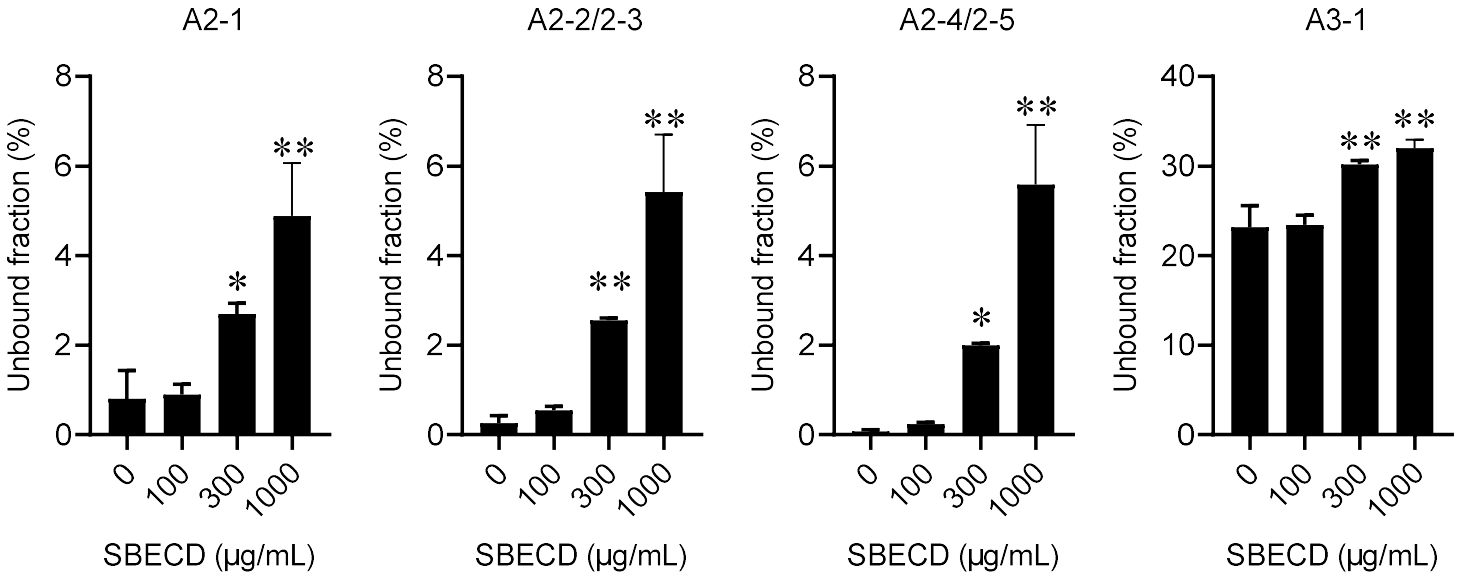


Figure 5


A2-1
A2-2/2-3
A2-4/2-5
A3-1
Unbound fraction (%)
SBECD (μg/mL)
0
100
300
1000
*
**