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

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Running head: Interaction between teicoplanin and SBECD

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Abstract

Patients undergoing hematopoietic stem cell transplantation (HSCT) often receive multiple antibiotics and antifungals concurrently, making it crucial to understand their potential pharmacokinetic interactions of these agents. 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). We performed a single-center retrospective analysis of patients who underwent HSCT and received oral and intravenous PSCZ during TEIC therapy. The associations between PSCZ administration and TEIC concentration-to-dose (C/D) ratios were evaluated using linear mixed-effects models. We also examined the effects of intravenous PSCZ and SBECD on TEIC pharmacokinetics in rats by assessing the area under the concentration–time curve (AUC) and urinary excretion of total TEIC and its components. In addition, molecular docking and in vitro protein-binding assays were conducted to investigate the interaction between TEIC and SBECD. In patients who underwent HSCT, TEIC C/D ratio was significantly lower following intravenous PSCZ administration than without administration. In contrast, the effect of oral PSCZ administration relative to non-administration was not statistically significant. In rats, intravenous PSCZ and SBECD decreased the AUC of TEIC and increased urinary excretion, particularly in the A_2 group. Docking simulations indicated that the hydrophobic side chain of TEIC $A_{2\text{-}2}$ fit within the SBECD cavity, and in vitro assays confirmed SBECD concentration-dependent increases in TEIC unbound fractions. The co-administration of intravenous PSCZ containing SBECD may reduce TEIC protein binding, thereby enhancing renal excretion.

Introduction

Patients who undergo hematopoietic stem cell transplantation (HSCT) are susceptible to bacterial and fungal infections owing to immunosuppression caused by conditioning chemotherapy before transplantation and subsequent immunosuppressive therapy. Consequently, multiple antibiotics and antifungal agents are often administered concomitantly to these patients for the 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 used in the treatment of methicillin-resistant *Staphylococcus aureus* infections, and is administered empirically when gram-positive bacterial infections are suspected. TEIC undergoes minimal metabolism and is eliminated primarily through the kidneys. Compared to vancomycin, TEIC exhibits a higher protein-binding rate, a larger volume of distribution, and a substantially longer half-life of approximately 83–168 h (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. To this end, fluctuations in TEIC exposure may result in treatment failure, highlighting the need to fully elucidate inter- and intra-individual factors that contribute to pharmacokinetic variability.

Azole antifungal agents are commonly administered to patients undergoing HSCT to prevent fungal infections. Posaconazole (PSCZ), an azole antifungal agent, is known for its potent antifungal activity and inhibition of the drug-metabolizing enzyme CYP3A and 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, PSCZ is unlikely to significantly affect the pharmacokinetics of renally excreted drugs. Patients undergoing HSCT often receive multiple antibiotics and antifungals concurrently; however, data on the pharmacokinetic interactions among these agents in this population remain limited.

Therefore, the aim of this study was to evaluate the effect of intravenous (i.v.) PSCZ co-administration on the plasma concentration of TEIC in patients undergoing HSCT. We assessed the reproducibility of this phenomenon using an animal model, and further identified sulfo-butyl ether-β-cyclodextrin (SBECD), a pharmaceutical excipient

contained in i.v. PSCZ, as a potential contributor to the reduction in plasma TEIC concentrations. Moreover, we predicted the formation of an inclusion complex of SBECD with TEIC, and evaluated the effect of SBECD on TEIC protein binding.

Materials and Methods

Effects of oral and intravenous PSCZ administration on TEIC plasma concentrations in patients who underwent HSCT

We conducted a single-center retrospective analysis of patients who underwent HSCT and received the tablet formulation (oral) and 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 available plasma TEIC concentration data under three conditions: without PSCZ administration, following oral PSCZ administration, and following i.v. PSCZ administration. This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (Approval No. R2470).

We extracted all available data on trough TEIC plasma concentrations from the hospital electronic medical database. Plasma TEIC concentrations 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 3 days after maintaining a constant dosage following TEIC loading, (ii) obtained at least 3 days after dosage adjustment, or (iii) obtained at least 3 days after switching the PSCZ formulation. We also collected data on 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 the association between PSCZ administration and changes in TEIC pharmacokinetics, the effects of PSCZ on the concentration-to-dose (C/D) ratio of TEIC were estimated using a linear mixed-effects model:

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

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

120 intercept (individual-level residual with mean zero and variance σ^2_γ), and ε is the
121 estimated residual error (with mean zero and variance σ^2_ε). I_{oral} = 1 if oral PSCZ was co-
122 administered, and 0 otherwise; $I_{intravenous}$ = 1 if i.v. PSCZ was co-administered, and 0
123 otherwise. The effects of PSCZ were further adjusted for age, sex, serum albumin level,
124 and eGFR, which were incorporated as independent covariates with fixed effects.
125 Analyses were performed using JMP software version 18 (SAS Institute Inc., Cary, NC,
126 U.S.A.)
127
128 Pharmacokinetics of TEIC in rats
129 Eight-week-old male Wistar/ST rats were purchased from the SLC Animal
130 Research Laboratories (Shizuoka, Japan) and maintained in accordance with the
131 guidelines for Animal Experiments of Kyoto University, Kyoto, Japan. The study was
132 approved by the Animal Research Committee of the Graduate School of Medicine,
133 Kyoto University, Kyoto, Japan (permit numbers: Medkyo 22119 and 23107). The rats
134 were housed in a specific pathogen-free facility, maintained in a temperature-controlled
135 environment with a 12-h light/dark cycle, and fed a standard diet and water ad libitum.
136 For the administration of TEIC and PSCZ to rats, the commercially available i.v.
137 formulations, Teicoplanin for Intravenous Infusion 200 mg (Towa) (Towa
138 Pharmaceutical Co., Ltd. Osaka, Japan) and Noxafil® for Intravenous Infusion 300 mg
139 (MSD K.K., Tokyo, Japan) were used. SBECD was purchased from ChemScene (NJ,
140 USA). All other reagents and solvents were of analytical or liquid chromatography-mass
141 spectrometry grade.
142 The rats were anesthetized with a combination of medetomidine, midazolam,
143 and butorphanol, and catheters were inserted into the left femoral vein and right femoral
144 artery using polyethylene tubing (SP-31; Natsume Seisakusho, Tokyo, Japan). Saline,
145 PSCZ (40 mg/kg PSCZ plus 890.67 mg/kg SBECD), or SBECD alone (890.67 mg/kg)
146 was administered through the femoral vein. These doses were set with reference to the
147 human equivalent dose in rats, where the dose per body weight is approximately six
148 times the human dose (8). Thirty minutes later, TEIC (20 mg/kg) was injected into the
149 femoral vein. Six rats per group were used in the experiment. PSCZ is highly
150 hydrophobic, making it difficult to dissolve in a solvent suitable for i.v. administration
151 without SBECD. Therefore, the PSCZ-alone group was not included in this study.

152 Blood samples were collected from the femoral artery at the end of TEIC administration
153 and 5, 15, 30, 60, 90, and 120 min thereafter. Plasma was separated by centrifugation.
154 Urine was collected from the bladder into a polyethylene tube for 120 min after TEIC
155 administration. Plasma and urine samples were deproteinized by adding four volumes of
156 methanol, followed by centrifugation at 10,000 × *g* for 5 min. A 50 μL aliquot of the
157 supernatant was mixed with 200 μL of methanol. Urine samples were further diluted
158 five-fold with methanol. Lastly, all samples were filtered through a 0.45 μm membrane
159 filter prior to analysis.
160 TEIC was quantified using a triple-quadrupole mass spectrometry system
161 (LCMS-8040; Shimadzu, Japan) equipped with an electrospray ionization source. The
162 mobile phases were 0.1% formic acid in water (phase A) and 0.1% formic acid in
163 acetonitrile (phase B). The gradient elution program was as follows: 0–1.0 min, 5% B;
164 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,
165 5% B. The flow rate was 0.25 mL/min, the column oven temperature was 60 °C, and the
166 injection volume was 5 μL. Chromatographic separation was achieved using an
167 ACQUITY UPLC BEH C18 column (50 × 2.1 mm, 1.7 μm particle size; Waters, USA).
168 Detection was performed in positive ion mode using multiple reaction monitoring.
169 Since the clinically used i.v. formulation of TEIC comprises five major components (A_{2-}
170 $_{1}$, A_{2-2}, A_{2-3}, A_{2-4}, and A_{2-5}), and one hydrolysis component (A_{3-1}) (Fig. 1), the following
171 ion transitions were monitored to detect each component: A_{2-1}, from *m/z* 939.7 to 314.2;
172 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},
173 from *m/z* 782.4 to 203.7 (9).
174 The area under the plasma concentration–time curve (AUC) and the urinary
175 excretion of TEIC were determined over 120 min after administration. The AUC and
176 urinary excretion were calculated for total TEIC, and each individual component.
177 Statistical analyses were performed using GraphPad Prism version 8.0 software
178 (GraphPad, San Diego, CA, USA). The data were analyzed using one-way analysis of
179 variance; a *P*-value < 0.05 was considered statistically significant.
180
181 Molecular docking simulation
182 Since TEIC A_{2-2} is the major component of the clinical formulation and its
183 conformation is crystallographically characterized, only this dominant analog was

184 considered for molecular modeling. The 3D structure of TEIC A_{2-2} was obtained from
185 the Protein Data Bank (ID: 4PJZ) (10). The structure of SBECD was constructed using
186 Avogadro software (ver. 1.2.0) (11) on the basis of the 3D structures of native β-CD that
187 was retrieved from the Protein Data Bank (ID: 3CGT). Based on previous reports (12),
188 the structure of SBECD was prepared by assuming that seven glucopyranose units were
189 substituted with sulfobutyl ether, namely four at position C2 on the secondary face
190 (residues 1, 3, 5, and 7) and three at position C6 on the primary face (residues 2, 4, and
191 6), in accordance with the average degree of substitution of the SBECD reagent (6.0-
192 7.1). The molecular geometries of TEIC A_{2-2} and SBECD were fed into GAMESS (ver.
193 2023 R1) (13) for geometry optimization using the semi-empirical quantum chemistry
194 method PM3. By treating the geometry-optimized structures of TEIC A_{2-2} and SBECD
195 as ligands and receptors, respectively, molecular docking to obtain complexes of TEIC
196 A_{2-2} with SBECD was performed with 100 runs using the Lamarckian genetic algorithm
197 in AutoDock 4.2 (14). The receptor and ligand were assigned Gasteiger partial charges
198 and the rotatable bonds were not defined. All other parameters were set to the default
199 values for AutoDock 4.2.
200
201 Effect of SBECD on TEIC protein binding in human serum
202 SBECD (40 mg/mL in distilled water) was diluted with human serum (Kojin
203 Bio, Saitama, Japan) to prepare serum samples containing 0, 100, 300, and 1000 μg/mL
204 of SBECD. These concentrations were within the range observed in clinical settings (15,
205 16). Aliquots of 380 μL of each serum sample were incubated at 37 °C for 30 min.
206 Subsequently, 20 μL of TEIC injection solution, prepared with distilled water to a
207 concentration of 0.8 mg/mL, was added to achieve a final concentration of 40 μg/mL.
208 This corresponded to the upper limit of the clinically targeted trough concentration of
209 TEIC. The samples were then incubated at 37 °C for 60 min, with gentle mixing for 10 s
210 every 10 min during incubation. After incubation, 300 μL of each sample was
211 immediately collected and filtered through an ultrafiltration membrane (30 kDa,
212 Millipore, Tokyo, Japan). TEIC calibration curves were generated using serum
213 subjected to the same ultrafiltration procedure used for the matrix. The concentration of
214 TEIC in the filtrate was quantified using the method described above, and the unbound
215 fraction was calculated relative to the concentration of 40 μg/mL. Data were analyzed

using one-way analysis of variance, and a P-value < 0.05 was considered statistically significant.

Results

Decreased TEIC plasma concentrations following i.v. PSCZ administration in patients who underwent HSCT

This study included eight patients who underwent HSCT and received both TEIC and PSCZ during the observation period. The plasma TEIC concentrations were measured under three conditions: without PSCZ administration, following oral PSCZ administration, and following i.v. 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 administration, 27 following oral administration, and 33 following i.v. administration. The data points per person ranged from a minimum of five to a maximum of 18. The 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) following oral PSCZ administration, and 2.23 (SD, 0.95) following i.v. administration (Fig. 2). A linear mixed-effects model demonstrated that the C/D ratio was significantly lower following i.v. PSCZ administration than without 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 i.v. PSCZ remained significant (estimate: -1.22; 95% CI, -1.84 to -0.60). This corresponds to a decrease of approximately 35% compared to 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 i.v. formulation of PSCZ is associated with reduced plasma TEIC concentrations. Because the dosage of PSCZ was identical regardless of the route of administration (300 mg/day), we focused on SBECD, which is present only in the i.v. formulation, as a potential factor influencing TEIC

248 pharmacokinetics. To test this hypothesis, rats were pretreated with either an i.v. PSCZ
249 formulation or SBECD followed by TEIC administration, and the AUC and urinary
250 excretion of TEIC were evaluated (Fig. 3). Compared to rats pretreated with saline,
251 those pretreated with either i.v. PSCZ or SBECD showed a significant decrease in TEIC
252 AUC and a significant increase in urinary excretion (Fig. 3A–C). No significant
253 differences were observed in the plasma concentrations immediately after
254 administration (Figure 3A) or significant differences in urine volume (Fig. 3D) between
255 the groups. Furthermore, the relative abundance of the individual components of the
256 TEIC formulation, $A_{2\text{-}1}$, $A_{2\text{-}2/2\text{-}3}$, $A_{2\text{-}4/2\text{-}5}$, and $A_{3\text{-}1}$, was determined. Following the i.v.
257 administration of PSCZ or SBECD, the AUC of the A_2 group significantly decreased,
258 whereas the urinary excretion significantly increased (Fig. 3E–G, 3I–K). In contrast, no
259 significant effects were observed for $A_{3\text{-}1}$ (Fig. 3H and 3L).
260
261 Molecular modeling of TEIC $A_{2\text{-}2}$ inclusion complex with SBECD
262 The abovementioned findings indicate that SBECD contributes to a reduction
263 in TEIC plasma concentration, with a greater impact on the A_2 group than $A_{3\text{-}1}$.
264 Structural differences exist between these groups because only the A_2 group possesses a
265 long carbon chain (Fig. 1). Furthermore, a previous study showed that a β-cyclodextrin
266 derivative, 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), potentially prevents the
267 hydrolysis of the glycosyl group with a hydrophobic side chain of dalbavancin, a
268 semisynthetic glycopeptide with an analogous molecular scaffold of TEIC (17).
269 Therefore, we hypothesized that SBECD accommodates the side chain of TEIC, thereby
270 inhibiting its binding to serum proteins. To test this postulation, we performed docking
271 simulations for TEIC $A_{2\text{-}2}$, a major analog of TEIC, against SBECD using AutoDock
272 software. Through 100 docking runs, we obtained two probable binding modes for the
273 TEIC $A_{2\text{-}2}$ complex with SBECD: the dimethyl terminus of the TEIC $A_{2\text{-}2}$ side chain was
274 directed towards the primary face of the SBECD molecule for Type I (Fig. 4A), and the
275 dimethyl terminus was directed towards the secondary face of the SBECD molecule for
276 Type II (Fig. 4B). Regardless of the binding mode, most of the TEIC $A_{2\text{-}2}$ hydrophobic
277 side chain, which contributes to an increased protein-binding rate, was accommodated
278 within the hydrophobic inner cavity of SBECD.
279

280 Effect of SBECD on TEIC protein binding

281 The above findings suggest that SBECD exerts a strong influence on TEIC
282 protein binding, particularly on the A_2 group. Therefore, we evaluated the unbound
283 fraction of TEIC in human serum containing clinically relevant concentrations of
284 SBECD (Fig. 5). The results demonstrated that the unbound fractions of both the A_2
285 group and $A_{3\text{-}1}$ increased in a concentration-dependent manner with increasing SBECD
286 concentration. Compared with the condition without SBECD, the unbound fractions of
287 $A_{2\text{-}1}$, $A_{2\text{-}2/2\text{-}3}$, $A_{2\text{-}4/2\text{-}5}$, and $A_{3\text{-}1}$ increased by 3.4-fold, 9.6-fold, 25.9-fold, and 1.3-fold,
288 respectively, at an SBECD concentration of 300 μg/mL.

289

290 **Discussion**

291 Multiple antibiotics and antifungal agents are often used concurrently in
292 patients undergoing HSCT, making it essential to fully understand the potential
293 interactions between these drugs. In this study, we demonstrated, for the first time, that
294 the co-administration of an i.v. formulation of PSCZ with TEIC in patients undergoing
295 HSCT resulted in reduced TEIC plasma concentration. A key strength of this study is
296 that the reproducibility of this phenomenon was confirmed by integrating clinical
297 observations with an animal model. Moreover, by focusing on the pharmaceutical
298 excipient SBECD, we further elucidated its impact on TEIC protein binding using in
299 vitro assays and the mode of inclusion complex formation through molecular modeling.

300 SBECD is a derivative of β-cyclodextrin, composed of seven glucose units
301 linked in a ring, with a hydrophobic inner cavity and a hydrophilic outer surface. This
302 structure enables the encapsulation of hydrophobic drugs, thereby improving their
303 aqueous solubility (18-20). Each vial of the i.v. PSCZ formulation (Noxafil® 300 mg)
304 contains 6,680 mg of SBECD. In general, cyclodextrin–drug inclusion complexes are
305 thought to have minimal effects on pharmacokinetics, as they dissociate rapidly after i.v.
306 administration (21-27). However, exceptionally stable complexes are known to
307 markedly alter drug elimination pathways. For instance, the rocuronium–sugammadex
308 complex exhibits a high stability constant, whereas rocuronium alone is excreted
309 through bile and rapidly eliminated in urine in the presence of sugammadex (21).
310 Similarly, drugs with an adamantane structure show particularly high affinity because of
311 their close fit with the cyclodextrin cavity (28), and urinary excretion rates have been

312 reported to increase from 0.1% to 37% in the presence of SBECD (29). In the current
313 study, rats administered with either the i.v. PSCZ formulation or SBECD alone
314 exhibited a significant increase in TEIC urinary excretion, supporting the interaction
315 between TEIC and SBECD in vivo.

316 Semisynthetic lipoglycopeptides, such as the TEIC A_2 group, telavancin,
317 dalbavancin, and oritavancin, exhibit high protein binding and consequently much
318 longer half-lives than vancomycin owing to their lipophilic side chains (30). Although
319 the binding affinity of TEIC for human serum albumin (HSA), the predominant serum
320 protein, has been reported (31) , its binding conformation remains unclear. Dalbavancin,
321 which shares a large structural similarity with TEIC, binds to HSA by inserting its
322 hydrocarbon chain into the hydrophobic pocket within subdomain IA of HSA,
323 composed entirely of nonpolar amino acids (32). Given that TEIC, despite isoform
324 differences, also possesses a long hydrocarbon chain and a conserved cyclic peptide
325 core, it is likely to bind albumin in a similar manner. This hypothesis is consistent with
326 our in vitro findings that showed a higher proportion of the unbound fraction of $A_{3\text{-}1}$
327 than that of the A_2 group. Furthermore, HP-β-CD has been shown to slowly hydrolyze
328 the glycosidic linkage between the mannosyl aglycone and hydrophobic side chain of
329 dalbavancin (17), suggesting that HP-β-CD interacts with and shields this region. The
330 use of HP-β-CD as a pharmaceutical excipient to enhance the solubility of telavancin
331 (Vibativ®) (33) and oritavancin (Kimyrsa®) (34) further supports our findings
332 regarding TEIC–CD interactions. $A_{2\text{-}2}$, $A_{2\text{-}3}$, $A_{2\text{-}4}$, and $A_{2\text{-}5}$ are the major components of
333 clinical TEIC formulations. In this study, SBECD significantly increased the unbound
334 fraction of TEIC, particularly in the A_2 group. These results suggest that the
335 hydrophobic cavity of SBECD accommodates much of the hydrophobic side chain of
336 TEIC A_2, thereby reducing protein binding and leading to decreased plasma
337 concentrations through enhanced renal excretion.

338 In patients who underwent HSCT, the C/D ratio of TEIC decreased by an
339 average of 1.2 when the i.v. formulation of PSCZ was administered, compared with no
340 administration. In other words, when TEIC was administered at 10 mg/kg/day, co-
341 administration of i.v. PSCZ resulted in an approximate 12 μg/mL reduction in TEIC
342 trough levels. However, this study had certain limitations. The clinical sample size in
343 this study was limited, and large-scale prospective studies are needed to evaluate the

magnitude of this effect more accurately. In addition, an assessment of how these plasma concentration changes affect the efficacy of TEIC should be conducted through pharmacokinetic-pharmacodynamic analyses. Moreover, since SBECD is widely used in injectable formulations beyond PSCZ, future studies should investigate potential interactions between TEIC and these SBECD-containing products, as well as with drugs possessing similar hydrophobic side chains.

Taken together, our findings suggest that the co-administration of i.v. PSCZ containing SBECD and TEIC may reduce the protein binding of the latter, 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.

Acknowledgements

This work was supported by the grant from the Nakatomi Foundation. The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

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469

470 **Figure legends**

471 Fig. 1. Chemical structures of teicoplanin (TEIC, left) and sulfo-butyl ether-β-
472 cyclodextrin (SBECD, right).
473
474 Fig. 2. Trough plasma concentrations of TEIC in patients who underwent hematopoietic
475 stem cell transplantation (HSCT) during periods without posaconazole (PSCZ)
476 administration, following PSCZ oral administration, and following PSCZ intravenous
477 administration. The TEIC concentration/dose (C/D) ratios were obtained from 83
478 plasma concentration measurements across eight patients: 23 who did not receive
479 PSCZ, 27 who administered oral PSCZ, and 33 who received intravenous (i.v.) PSCZ.
480 Bars indicate the mean C/D ratio, and error bars represent standard deviations.
481
482 Fig. 3. Pharmacokinetics of TEIC in rats. Male Wistar/ST rats (8 weeks old) received an
483 intravenous injection via the femoral vein of saline (Control), PSCZ intravenous
484 formulation (i.v. PSCZ), or SBECD alone (SBECD). Thirty minutes later, TEIC was
485 administered intravenously. (A–D) The area under the plasma concentration–time curve
486 (AUC) and urinary excretion of TEIC were evaluated over 120 min after TEIC
487 administration. (E–L) The AUC and urinary excretion of individual TEIC components
488 were evaluated and expressed as relative values to the Control group. $*P < 0.05$, $**P <$
489 0.01, significantly different from the Control group (n = 6 per group).
490
491 Fig. 4. Estimated binding modes of TEIC $A_{2\text{-}2}$ with SBECD. The lowest TEIC $A_{2\text{-}2}$
492 binding energy conformations for SBECD in the most probable docking clusters from
493 100 runs. The dimethyl terminus of the TEIC $A_{2\text{-}2}$ side chain is directed towards the
494 primary face of the SBECD molecule in Type I (A) and is directed towards the
495 secondary face of the SBECD molecule in Type II (B). The left, middle, and right
496 panels show the front, side, and back views as the chemical structure of TEIC in Figure
497 1, respectively.
498
499 Fig. 5. Unbound fraction of TEIC in human serum. Human serum containing various
500 concentrations of SBECD was supplemented with TEIC. The unbound fraction of each
501 TEIC component was determined. $*P < 0.05$, $**P < 0.01$, significantly different from

502 the group without SBECD (“0”) (n = 3 per group).

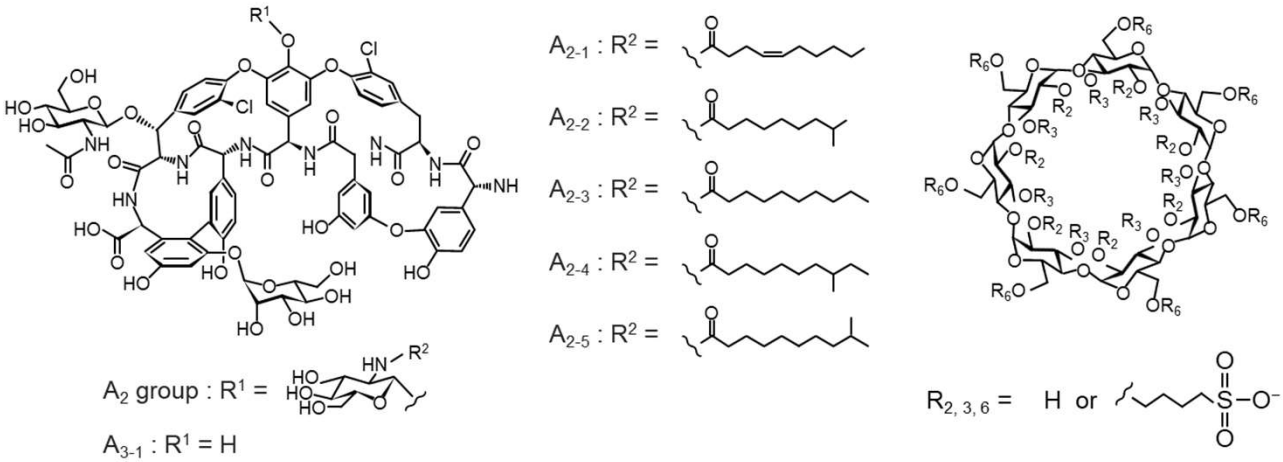
503

504 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 administration	23
Administered oral posaconazole	27
Administered intravenous posaconazole	33

505 S.D., standard deviation. Posaconazole was administered at a dose of 300 mg/day
506 regardless of body weight or route of administration.
507

Fig. 1



Teicoplanin (TEIC)

Sulfo-butyl ether-β-cyclodextrin (SBECD)

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

Fig. 2

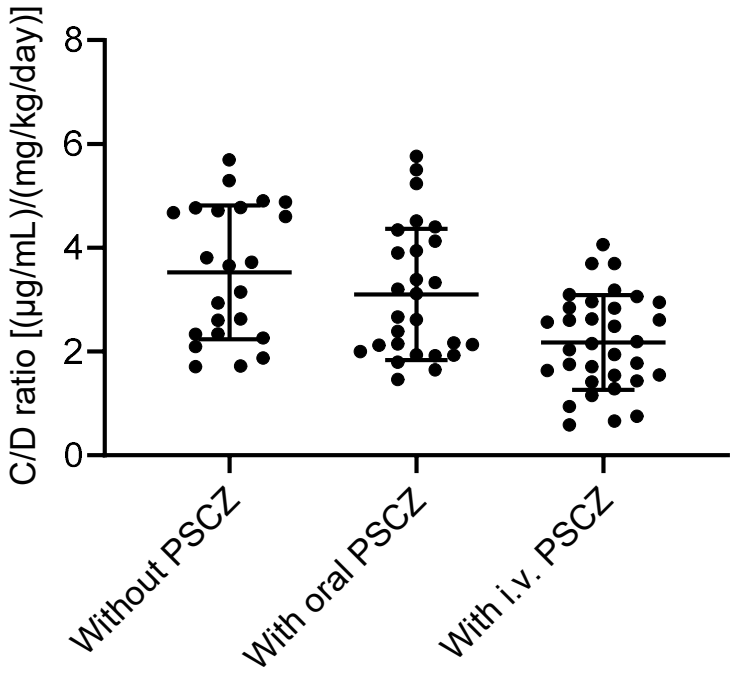


Fig. 2. Trough plasma concentrations of TEIC in patients who underwent hematopoietic stem cell transplantation (HSCT) during periods without posaconazole (PSCZ) administration, following PSCZ oral administration, and following PSCZ intravenous administration. The TEIC concentration/dose (C/D) ratios were obtained from 83 plasma concentration measurements across eight patients: 23 who did not receive PSCZ, 27 who administered oral PSCZ, and 33 who received intravenous (i.v.) PSCZ. Bars indicate the mean C/D ratio, and error bars represent standard deviations.

Fig. 3

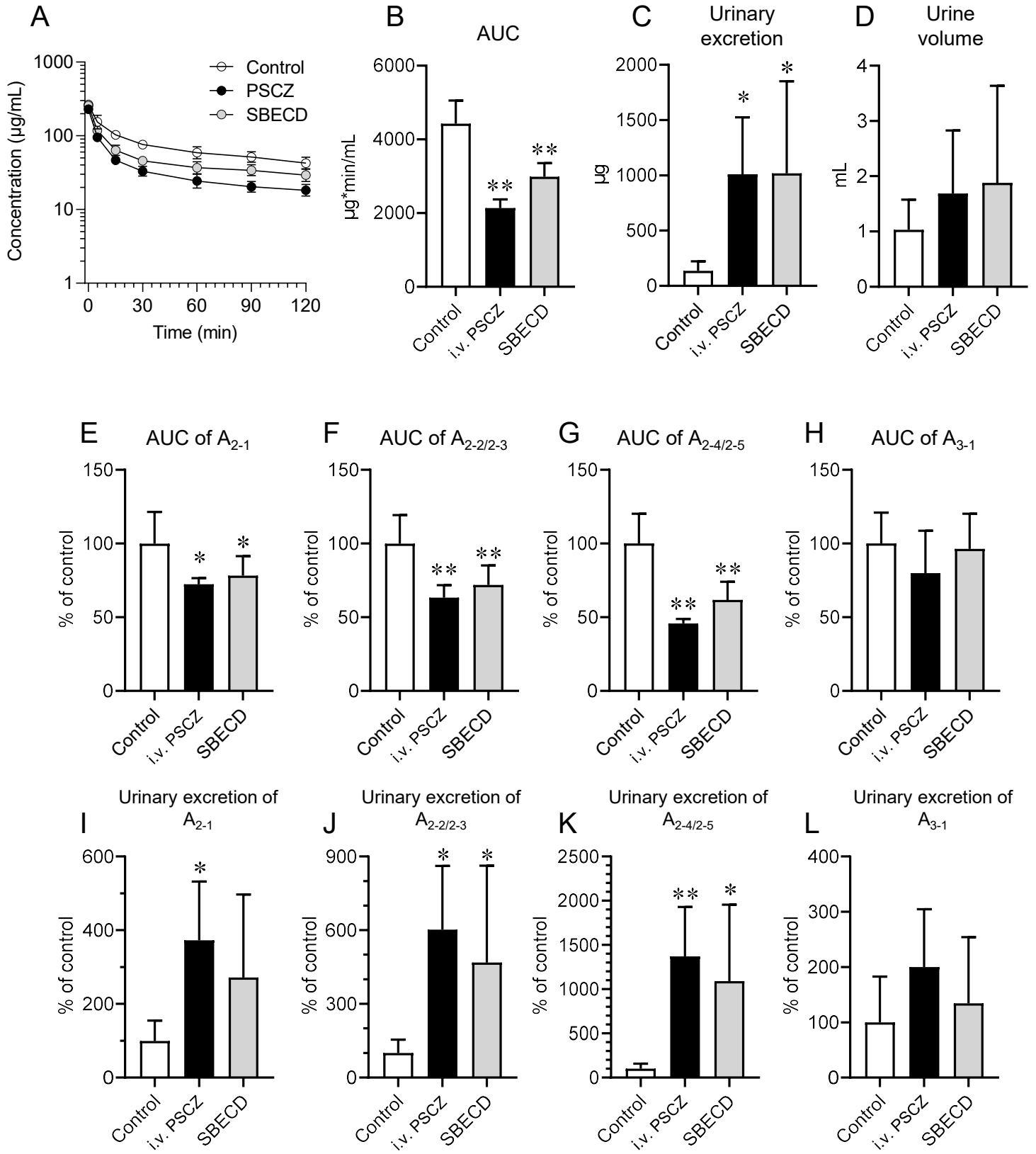


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Fig. 4

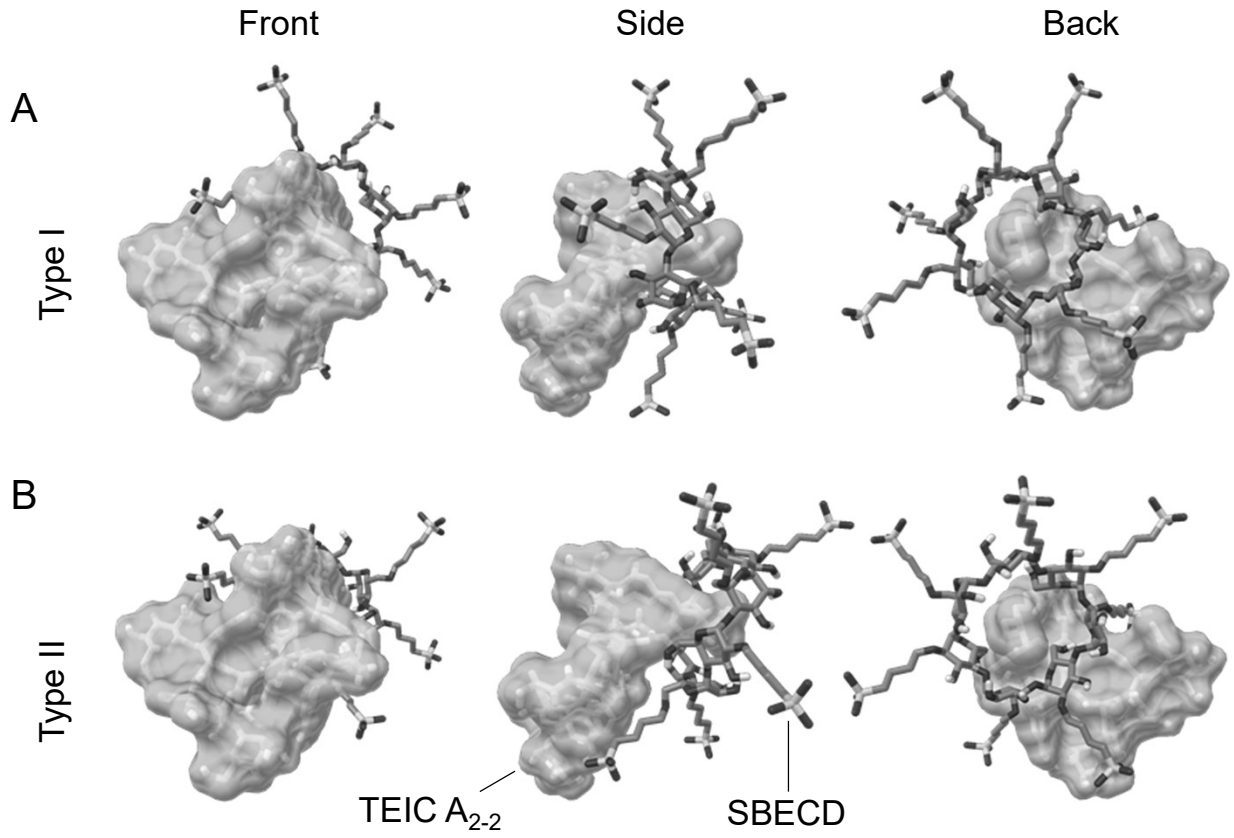

Fig. 4. Estimated binding modes of TEIC A_{2-2} with SBECD. The lowest TEIC A_{2-2} binding energy conformations for SBECD in the most probable docking clusters from 100 runs. The dimethyl terminus of the TEIC A_{2-2} side chain is directed towards the primary face of the SBECD molecule in Type I (A) 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 the chemical structure of TEIC in Figure 1, respectively.

Fig. 5

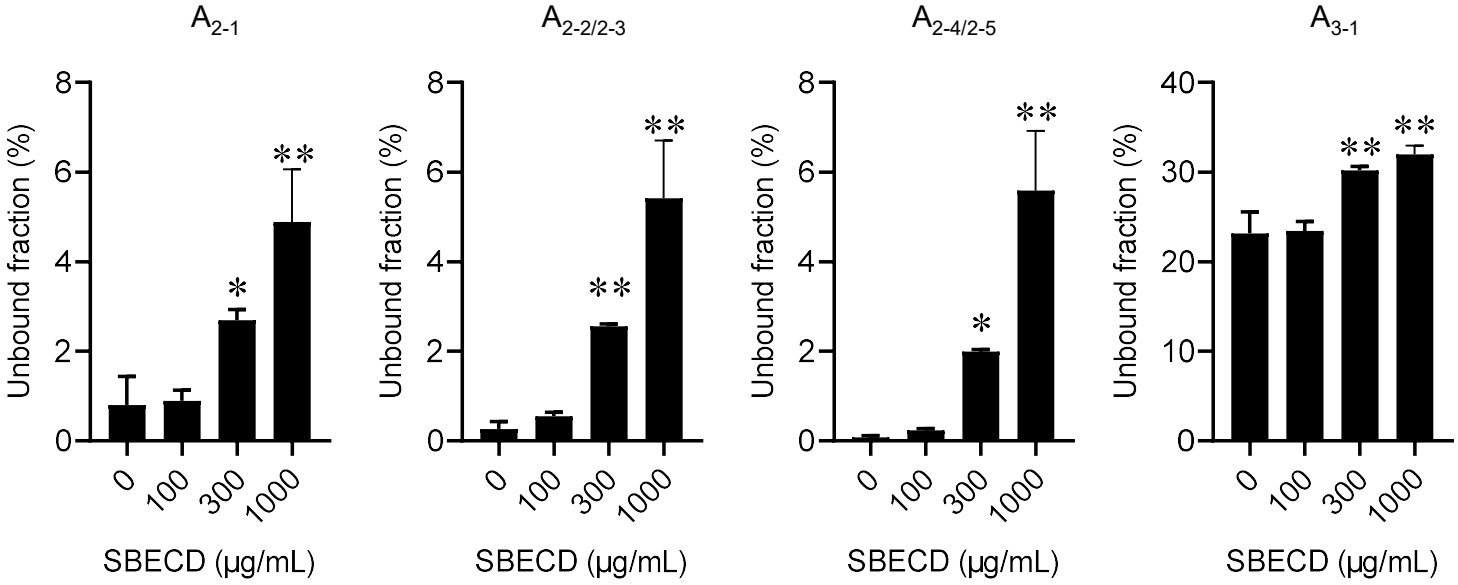

Fig. 5. Unbound fraction of TEIC in human serum. Human serum containing various concentrations of SBECD was supplemented with TEIC. The unbound fraction of each TEIC component was determined. *P < 0.05, **P < 0.01, significantly different from the group without SBECD ("0") (n = 3 per group).