Elimination of teicoplanin by adsorption to the filter membrane during haemodiafiltration: Screening experiments for linezolid, teicoplanin and vancomycin followed by in vitro haemodiafiltration models for teicoplanin

Elimination of teicoplanin by adsorption during continuous hemodiafiltration

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Abstract

Introduction. Anti-MRSA agents may be eliminated during continuous hemodiafiltration (CHDF), not only by diffusion and ultrafiltration but also by adsorption onto hemofilters, which may be affected by the binding of agents to albumin. The present study was aimed to investigate the affinity of anti-MRSA agents to hemofilters and pharmacokinetic properties of teicoplanin during CHDF.

Methods. As a screening experiment, linezolid, teicoplanin and vancomycin were dissolved in Krebs-Ringer's bicarbonate solution and shaked in a flask with 3 kinds of filter membrane piece; polysulfone (PS), polyacrylonitrile (PAN), and polymethylmethacrylate (PMMA). The *in vitro* model of continuous hemodiafiltration consists of a 1 L beaker containing Krebs-Ringer's bicarbonate solution with or without human albumin (albumin concentration: 0, 3 g/dL) as an artificial plasma. The solution containing teicoplanin at an initial concentration of 50 μg/mL was circulated at a flow rate of 100 mL/min through three kinds of hemofilters. The flow rates of dialysate and ultrafiltrate were 500 mL/h, respectively. Teicoplanin concentrations of "plasma" and ultrafiltrate were determined by HPLC.

Results. In the screening experiment, teicoplanin was predominantly adosorbed onto PS and PMMA membranes. Teicoplanin was eliminated mainly by adsorption during continuous hemodiafiltration using PS and PMMA hemofilters. The PS and PMMA eliminated teicoplanin more rapidly than PAN. The presence of albumin had a significant but small influence.

Conclusions. We should adjust the dosing of teicoplanin by close monitoring during CHDF using PS or PMMA. Present recommendations of teicoplanin dosing should be re-evaluated in patients on CHDF by a future clinical study.

Keywords: absorption; albumin, continuous hemodiafiltration; hemofilters; teicoplanin

Introduction

Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents are frequently administered for the treatment of severe infections or sepsis caused by MRSA in critically ill patients who are often complicated with acute renal dysfunction. Hemodiafiltration (HDF) is widely applied to critically ill patients with acute kidney and other organ dysfunctions. Continuous hemodiafiltration (CHDF) has a minor influence on the hemodynamics and thus may be used in critically ill patients with unstable hemodynamics in the intensive care unit. In patients receiving HDF or CHDF, the optimal dose of antimicrobiotics including anti-MRSA agents should be determined by considering the renal function of patients as well as by estimating the clearance by the filter membrane [1,2].
Additionally, anti-MRSA agents have different affinities to plasma albumin. For instance, teicoplanin is bound to plasma albumin at the highest rate (90%) [3]. It has been assumed that free drugs unbound to albumin are eliminated by diffusion or ultrafiltration in HDF [4,5].
Evidence has been accumulating that some drugs including anti-MRSA agents may be eliminated during HDF or CHDF not only by diffusion and ultrafiltration but also by adsorption onto filter membranes [6-8]. The issue of antibiotic adsorption to haemofilters is a largely neglected but important area of research. Some drugs and albumin has been reported to interact with filter membranes [9].
Taken together, the influence of HDF or CHDF on pharmacokinetics of anti-MRSA drugs are suspected to depend partially on filter membrane and plasma albumin. In the present study, we first compared the affinity of anti-MRSA agents to various filter membrane in a simple screening experiment. Then, we investigated the effects of filter material and plasma albumin on teicoplanin elimination by adsorption onto filter membranes in an *in vitro* CHDF circuit model, since there are considerable technical and ethical problems which make the measurement of adsorption difficult in a clinical setting or in vivo.

Materials and Methods

Screening for anti-MRSA agent with high affinity to filter membrane

We firstly compared the affinity of anti-MRSA agents to three kinds of hemofilters, i.e. polyacrylonitrile (PAN) (APF-06S, Asahi Kasei Kuraray Medical, Japan), polysulfone (PS) (AEF-07, Asahi Kasei Kuraray Medical, Japan) and polymethylmethacrylate (PMMA) (CH-0.6N, Toray Medical, Japan). We applied linezolid, teicoplanin or vancomycin as an anti-MRSA agent. As shown in Figure 1, the anti-MRSA agents were dissolved in 50 ml of Krebs-Ringer-Bicarbonate (KRB) solution in Erlenmeyer flask. The pH of KRB solution was adjusted at 7.4 and maintained with 5% carbon dioxide gas mixture. The concentration of each anti-MRSA agent was set to 20 μg/ml for linezolid, 50 μg/ml for teicoplanin and 50 μg/ml for vancomycin, respectively. The filter membranes were first primed with KRB at a transmenbrane pressure to obtain a sufficient filtration fluid, and then were cut into 5 mm pieces. The pieces were added to the solution. The flask was

incubated for 60 min in a 37ºC water bath. Then the concentrations of each anti-MRSA agent before and after the incubation were determined by the high-performance liquid chromatography (HPLC) system (described in detail in other section). Then adsorption rate of each drug was calculated using the following equation:

$$Adsorption\ rate = \frac{C_0 - C_{60}}{C_{60}} \times 100\ (\%)$$

Where C_0 is the concentration of the drug at 0 min and C_{60} is the concentration of the drug at 60 min. The anti-MRSA agent solutions represented 1/240 of total extracellular fluid (12 litters) and hemofilter surface area clinically used (0.6 m^2 or 0.7 m^2).

In vitro CHDF circulation experiment for teicoplanin

The *in vitro* model of CHDF consists of 1 litter beaker containing KRB with or without human albumin (Figure. 2). The CHDF was performed using an ACH-10 system (Asahi Kasei Kuraray Medical, Japan). Albumin concentration was set to 3 g/dl using 25% human serum albumin (CSL Behring, Japan). The KRB containing teicoplanin at an initial concentration of 50 □g/ml was circulated at a flow rate of 100 ml/min through three filter membranes, i.e. PS, PAN and PMMA and the circuits (CHD-400N, Asahi Kasei Kuraray Medical, Japan). The pH of KRB solution was adjusted at 7.4 and continuously equilibrated with a 5% carbon dioxide gas mixture. We discarded 200 ml of KRB to wash the circuit. The flow rates of dialysate, ultrafiltrate and fluid replacement were 500 ml/h, respectively. After teicoplanin was added to the beaker, the system was allowed to be primed for 5 min at a flow rate of 100 ml/min. Following the priming, dialysis and ultrafiltration was started (time point 0 min).

The KRB samples for assay were taken at the inlet and outlet of the hemofilter simultaneously with filtrate samples at time points of 0, 15, 30, 45, 60, 90 and 120 min. Additionally, KRB samples were taken before the priming (baseline, BL) and total filtrate samples at time point 120 min. These samples were stored at -80ºC and the concentrations of teicoplanin were determined by HPLC system later. Then adsorption rate was obtained according to the following equation:

$$Adsorption\ rate = \frac{C_{BL} \times 1.2 - C_{200\ ml} \times 0.2 - C_{F\ Total} \times V_{F\ Total} - C_{120} \times V}{C_{BL} \times 1.2} \times 100\ (\%)$$

Where C_{BL} is the concentration of teicoplanin at BL, $C_{200\ ml}$ is the concentration of teicoplanin in discarded 200 ml KRB, $C_{F\ Total}$ is the concentration of teicoplanin in total filtrate at 120 min, $V_{F\ Total}$ is the volume of total filtrate at 120 min, C_{120} is the concentration of teicoplanin at the inlet of the filter membranes, and V is the total volume of KRB.

The CHDF clearance which represents elimination by adsorption as well as diffusion and ultrafiltration was calculated by following equation:

$$CL_{CHDF} = k_e \bullet V_d$$

Where k_e is elimination rate constant and Vd is the distribution volume of teicoplanin, ie., the volume of KRB used in this system (= 1 litter). The k_e was estimated from the initial slope of the concentration versus time curve in semi-logarithmic plot.

Simple circulation without filtration or dialysis for teicoplanin

To confirm the absorption of teicoplanin onto membrane filters and eliminate the effect of dialysis and filtration, we performed simple circulation experiment. The simple circulation model consists of 1 litter beaker containing KRB without human albumin. The KRB containing teicoplanin at an initial concentration of 50 μg/ml was circulated at a flow rate of 100 ml/min without filtration and dialysis through the three filter membranes.
The KRB samples for assay were taken at the inlet and outlet of the filter membranes simultaneously at time points of 0, 15, 30, 45, 60, 90 and 120 min. Additionally, KRB samples were taken before equilibration. These samples were stored at -80ºC and the concentrations of teicoplanin were determined by HPLC system later. To evaluate the extent of teicoplanin absorption onto circuit, we performed similar experiment without filter membrane. In the sham group without filter membranes, KRB containing teicoplanin was circulated through the CHDF circuit excluding the filter membranes.

Determination of anti-MRSA agents using HPLC

The concentrations of anti-MRSA agents were determined using HPLC method. This system was composed of LC-10AD pump (Shimadzu, Japan), Shim-pack CLC-ODS (C_{18}, 150 × 6.0 mm) column (Shimadzu, Japan), SIL-10A auto injector (Shimadzu, Japan), CTO-10AC column oven (Shimadzu, Japan), SPD-6A UV spectrometric detector (Shimadzu, Japan) and C-R8A chromatopac integrator (Shimadzu, Japan).
The concentration of linezolid was determined by a modified HPLC technique [10]. Briefly, during the mobile phase, a mixture of acetonitrile and 50 mM sodium acetate buffer adjust to pH 4.0 (25:75, v/v) was pumped at a rate of 1.0 ml/min. The UV absorbance of eluent was monitored at 253 nm. The temperature of the column was maintained at 40ºC. Sample treatment involved vortex-mixing of 100 μL samples with 200 ml acetonitrile containing 50 μg/ml mephenesin (internal standard, IS) in a 1.5 ml centrifuge tube and centrifugation at 10,000 g for 5 min (4ºC). Two hundred μl aliquot of the supernatant liquid was transferred into a HPLC auto injector vial for injection of 20 μl onto the column.
The concentration of teicoplanin was measured by HPLC with slight modifications to method previously described [11]. The mobile phase consisted of acetonitrile / 50 mM sodium dihydrogen

phosphate aqueous solution (28:72, v/v) pumped at a rate of 1.5 ml. Teicoplanin was detected at a wavelength of 218 nm. The temperature of the column was maintained at 40ºC. Two hundred μl of distilled water and 50 μL of 50 μg/ml 5-(4-hydroxyphenyl)-5-phenylhydantoin (IS) methanol solution were added to 50 μl of samples, and then 400 μl of acetonitrile was added to precipitate proteins. After centrifugation (5 min, 10,000 g, 4 ºC), 600 μl of the supernatant was transferred to another centrifuge tube and 10 μl of 2 M HCl and 400 μl of chloroform were added, and then vortexed and centrifuged (5 min, 10,000 g, 4 ºC). Fifty μl of the obtained aqueous layer was injected into the HPLC system described above.

The concentratin of vancomycin was determined by HPLC with a modified method of Luksa J et al. [11]. The mobile phase was prepared by premixing acetonitrile and 50 mM sodium dihydrogen phosphate buffer (pH 2.5) in a 10:90 (v/v) ratio, and pumped through the column at a flow rate of 1 ml/min. Separated components were detected at 230 nm and the temperature of the column was maintained at 40ºC. Two hundred μl of samples were mixed with 50 μl of 20 μg/ml caffeine (IS) aqueous solution and 10 μl of 60% perchloric acid. The mixture was vortexed and then added with 10 μl of 6 M KCL . After centrifugation (5 min, 10,000 g, 4 ºC), 200 μl of the supernatant was transferred to another centrifuge tube and added with 400 μl of diethyl, and then vortexed and centrifuged (5 min, 10,000 g, 4 ºC). One hundred μl aliquot of the aqueous layer was transferred into a HPLC auto injector vial for injection of 50 μl onto the column.

Statistical analysis

Data are expressed as mean ± SE. One-way or two-way Analysis of variance (ANOVA) was applied for non-repeated measurement. Repeated measures ANOVA followed by Tukey-Kramer test were applied for repeated or serial determinations. Statistical significance was reached when $p<0.05$. The differences and effects were considered to be significant when p value was less than 0.05.

Results

Screening for anti-MRSA agent with high affinity to filter membrane

Fig. 3 represents the adsorption rate of anti-MRSA agents onto the three different filter membranes in the screening experiment. When compared with the absorption rate of each drug to the blank applying no filter membrane, teicoplanin was adsorbed significantly by PS and PMMA membranes. Linezolid and vancomycin were not absorbed by any filter membrane. Therefore, we focused on teicoplanin to conduct *in vitro* CHDF experiment.

In vitro CHDF experiment using teicoplanin with or without albumin

To confirm the absorption of teicoplanin onto the filter membrane under the condition of CHDF, *in vitro* CHDF experiment using teicoplanin was performed. Furthermore, to examine the effects of albumin on absorption of teicoplanin to filter membrane, we conducted in vitro CHDF experiment with or without albumin. Fig. 4 shows the time course of teicoplanin concentration throughout *in vitro* CHDF experiment with albumin. In the both experiments with and without albumin, the concentration of teicoplanin was consecutively decreased in any filter membrane and the decrease in teicoplanin concentration was significantly different among the three filter membranes. The extent of the decline was largest in PMMA and smallest in PAN membrane (Two-way repeated measures ANOVA followed by Tukey-Kramer test, $p < 0.05$).

PK parameters were summarized in Table 1. When the data were analyzed by two-way ANOVA, the CHDF clearance (CL_{CHDF}) was significantly affected by filter membrane ($p < 0.01$) and albumin ($p < 0.01$). There was a significant interaction of filter membrane and albumin ($p < 0.01$). The CL_{CHDF} was largest in PMMA membrane in the absence of albumin and was smallest in PAN membranes (Tukey-Kramer test, $p < 0.01$). Addition of albumin into KRB significantly decreased the CL_{CHDF} for all the filter membranes (Tukey-Kramer test, $p < 0.05$).

As shown in Table1, the adsorption rate of teicoplanin on to each filter membrane with or without albumin in *in vitro* CHDF experiment. Independent of the existence of albumin, the absorption rates of teicoplanin were significantly high in PS and PMMA filter membrane as compared with PAN membrane. The PMMA membrane has the highest binding capacity to teicoplanin, while PAN membrane has a negligible binding capacity. Addition of albumin into KRB slightly but significantly decreased the adsorption rate of teicoplanin onto PS and PMMA membranes (Tukey-Kramer test, $p < 0.05$). The adsorption rate of teicoplanin was significantly influenced by filter membrane ($p < 0.01$) and albumin ($p < 0.01$), indicating a significant interaction of filter membrane and albumin ($p < 0.01$).

Simple circulating model without filtration or dialysis

To confirm the absorption of teicoplanin onto membrane filters and eliminate the effect of dialysis and filtration, we performed simple circulation experiment. Moreover, to evaluate the extent of teicoplanin absorption onto circuit, the same experiment without filter membrane was conducted as a control group. Fig. 5 shows the time course of the teicoplanin concentration during a simple circulation. In control experiment, the concentration of teicoplanin was maintained throughout the experiment, indicating that the adsorption of teicoplanin to circuit is little. Compared with the control experiment, circulation through three filter membrane significantly decreased teicoplanin concentration (repeated measures ANOVA followed by Tukey-Kramer test, $P < 0.01$). The extent of

the decrease is largest in PMMA and smallest in PAN. The adsorption of teicoplanin onto filter membranes was confirmed in a simple circulating model without filtration or dialysis.

Discussion

In the present study, we first screened for anti-MRSA agent with high affinity to filter membrane in a shaken flask containing pieces of filter membrane and KRB solution. Since the absorption may occur within the wall or pores of the membrane as well as on the surface, we carefully primed the entire filters with KRB before cutting them into pieces. Teicoplanin was significantly and predominantly adsorbed by PS and PMMA membranes. Either linezolid or vancomycin was not significantly absorbed by any filter membrane. Recent studies have shown that vancomycin is adsorbed to hemodialysis membrane [25,26] . The discrepancy between these reports and ours may be explained by the differences in experiment method. Our screening model was very simple and excluded the effect of perfusion and transmenbrane pressures on the adsorption of anti-MRSA agents.

Since teicoplanin has the highest affinity to filter material, we investigated the influence of filter membrane and plasma albumin on teicoplanin elimination by adsorption onto filter membrane. The major finding of our study is that teicoplanin is significantly adsorbed by PS and PMMA filter membranes but not by PAN membrane. This property of teicoplanin was confirmed by 3 series of experiment as follows. Firstly, in the screening experiment, teicoplanin was a unique anti-MRSA agent binding to PMMA and PS membranes. Secondly, in the *in vitro* CHDF experiment, we demonstrated that high affinity of teicoplanin to PS and PMMA membranes may attribute to a large CL_{CHDF} when teicoplanin is administered during CHDF using PS and PMMA membrane. Finally, in a circulating model without filtration and dialysis, we showed that simple circulation through PMMA and PS membranes causes a significant and sufficient decrease in teicoplanin concentration. Since teicoplanin binds to plasma albumin at a rate of 90% [2], we investigated the effect of albumin on the PK parameters of teicoplanin in the *in vitro* CHDF experiment. When albumin was added to KRB solution, the CL_{CHDF} was greatly reduced in all the membrane tested. However, the addition of albumin exerted a significant but small effect on the adsorption rate. It has been shown that drugs with a high binding rate to albumin are eliminated defectively by diffusion and ultrafiltration [4, 5]. It is suggested that albumin attenuates the teicoplanin elimination mainly by affecting the diffusion and ultrafiltration through the membranes. A similar observation has been reported by Oborne et. al. that the presence of albumin decreases the amount of fluconazole adsorbed by PS and polyamide membranes [9].

In accordance to the results of present study, Menth et al. reported that teicoplanin may be eliminated by adsorption to several dialysis membranes, including PAN, PS and PMMA [13]. Clinical evidence has been accumulated that elimination of teicoplanin by hemodialysis and / or hemofiltration may be dependent on the applied membrane [2,6, 14-17]. The therapeutic drug

monitoring-guided dosage of teicoplanin is required for the patients treated with blood purification [14]. Considering the results of present study, it is necessary to adjust the dosage and the timing of teicoplanin administration during CHDF using PS or PMMA membrane. It may be considered that PAN instead of PS or PMMA should be selected as a filter membrane when teicoplanin administration is needed during CHDF. A high affinity to some filter membranes has been reported for other antibiotics [7-9, 18-20].

One of the proposed mechanisms by which some drugs bind to filter membranes is the electrostatic coupling of membranes and drugs that depends on the electric charges of membranes and drugs. Teicoplanin has carboxyl and amino terminals with pKs of 3.1 and 7.1, respectively. It is charged negatively at a physiological pH of 7.4. PS membrane has no net charge, while PMMA and PAN membranes have a negative charge [21, 22]. Therefore, the electrostatic coupling may not explain whether teicoplanin is predominantly adsorbed by PMMA and PS membranes. Teicoplanin is a glycopeptide whose structure resembles to that of protein. Since various proteins and polypeptides including □$_2$-microglobulin [23] and cytokines [24] binds to PMMA membrane, a non-specific mechanism may be involved in the binding of teicoplanin to PMMA membrane.

Limitations

Since the present study was conducted using *in vitro* model, the results of present study should be clinically confirmed. Critically ill patients receive various drugs and the concentrations of many biologically active substances are elevated in their plasma. teicoplanin and those substances may interact with albumin and filter membrane. We set the initial concentration of teicoplanin at 50 μg/mL, considering a Cmax value obtained by a common clinical dosage. The Cmax of teicoplanin may be higher when loading dose is applied. A higher concentration of teicoplanin may affect the adsorption rate. Furthermore, the parameters of CHDF including Q_F may vary among institutes and countries. These parameters may also influence the adsorption rate.

Our data suggests a clinical study is needed to re-evaluate current recommendations

Conclusions

Teicoplanin was eliminated mainly by adsorption during CHDF using PS and PMMA hemofilters. The PS and PMMA eliminated teicoplanin more rapidly than PAN. The presence of albumin had a significant but small influence. It may be necessary to adjust the dosage and the timing of teicoplanin administration by a close monitoring of drug concentration during CHDF using PS or PMMA membrane. A large clinical study is needed to confirm our in vitro observations and present recommendations of teicoplanin dosing should be re-evaluated in patients on CHDF.

List of abbreviations

ANOVA, Analysis of variance; CHDF, Continuous hemodiafiltration; HDF, Hemodiafiltration; HPLC, High-performance liquid chromatography; KRB, Krebs-Ringer's bicarbonate; PAN, Polyacrylonitrile; PMMA, Polymethylmethacrylate;. PS, Polysulfone.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Table 1 Effects of filter membrane and albumin on CHDF clearance and adsorption rate in *in vtro* CHDF experiment

filter membranes	Albumin = 0 g/dL		Albumin = 3 g/dL	
	CL_{CHDF} (mL/min)	Adsorption rate (%)	CL_{CHDF} (mL/min)	Adsorption rate (%)
PAN	12.6 ± 0.6	0.4 ± 0.2	6.7 ± 0.5	3.7 ± 1.3
PS	50.6 ± 1.5	69.8 ± 0.5	27.8± 0.4	61.4 ± 2.8
PMMA	60.8 ± 2.7	89.4 ± 1.4	26.7 ± 0.6	75.6 ± 1.1

Each value represents the mean ± S.E. (n = 3). The CHDF clearance (CL_{CHDF}) and adsorption was estimated as described in the "Materials and Methods". CL_{CHDF} was significantly affected by filter membrane and albumin ($p < 0.01$, two-way ANOVA). There was a significant interaction of filter membrane and albumin ($p < 0.01$, two-way ANOVA). The adsorption rate of TEIC was significantly different among the three filter membranes (PMMA > PS > PAN, two-way ANOVA followed by Tukey-Kramer test, $p < 0.01$). Addition of albumin significantly decreased adsorption rate ($p < 0.05$).

Figures

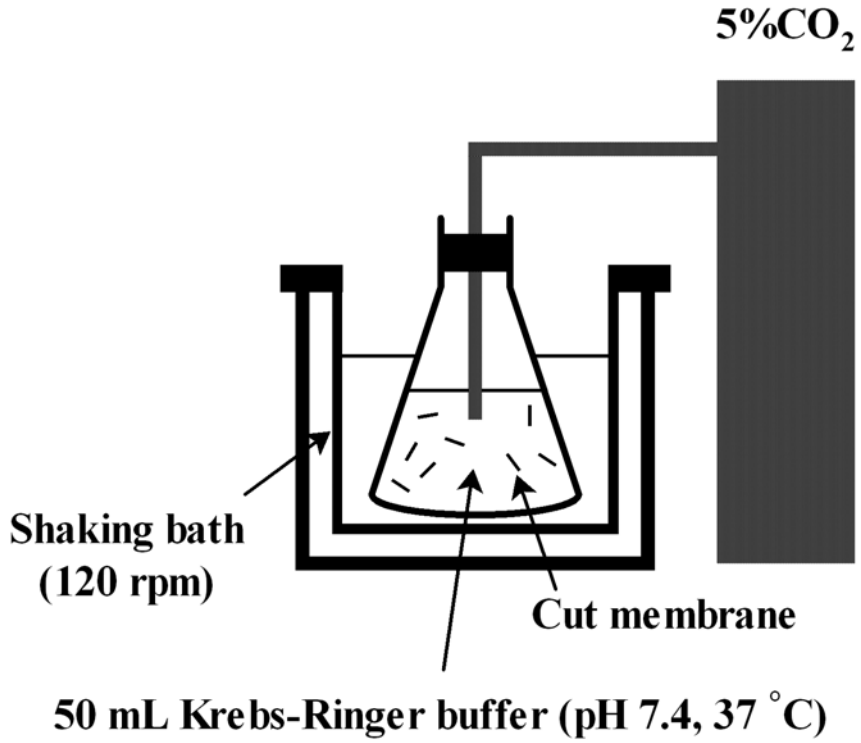

Figure 1: Device used in the screening experiment.

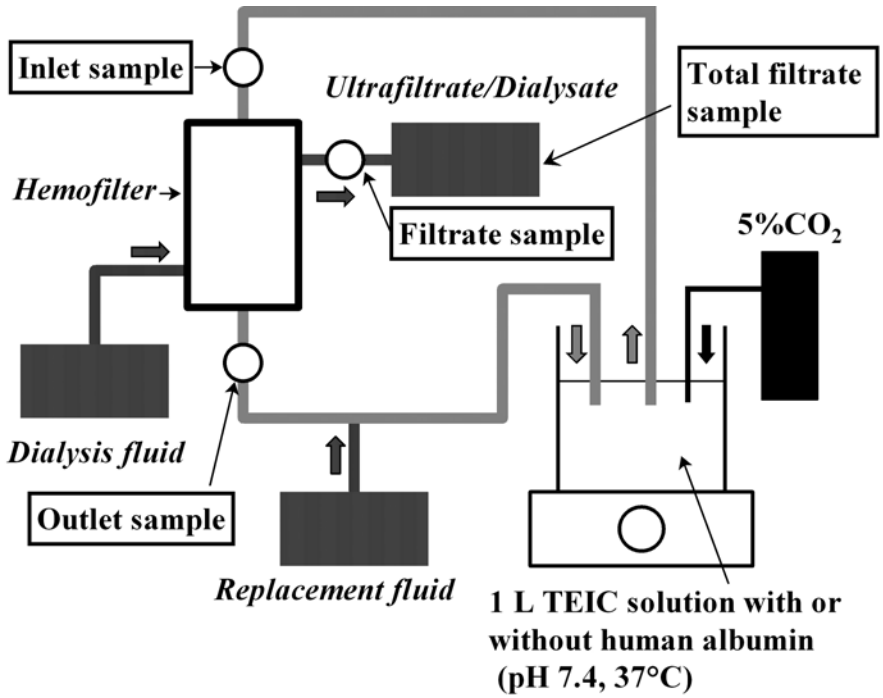

Figure 2: Circuit model of *in vitro* CHDF and sampling points.

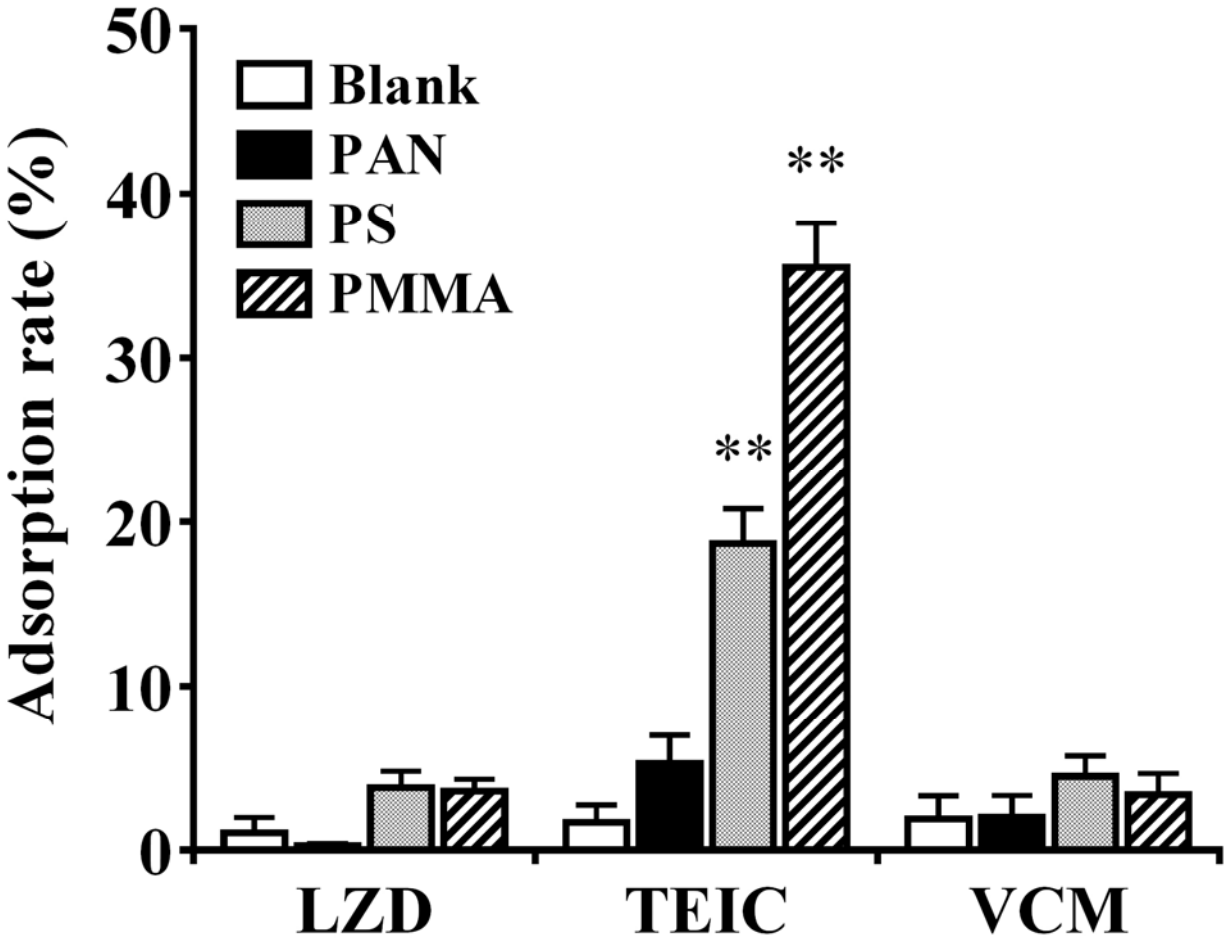

Figure 3: Adsorption rate of anti-MRSA agents onto three filter membrane in screening experiment.
Adsorption rate was calculated at the end of experiment (60 min). Each column with vertical bar represents the means ± S.E. (n = 6). ** significantly different from the blank (one-way ANOVA followed by Tukey-Kramer test, $p < 0.01$)

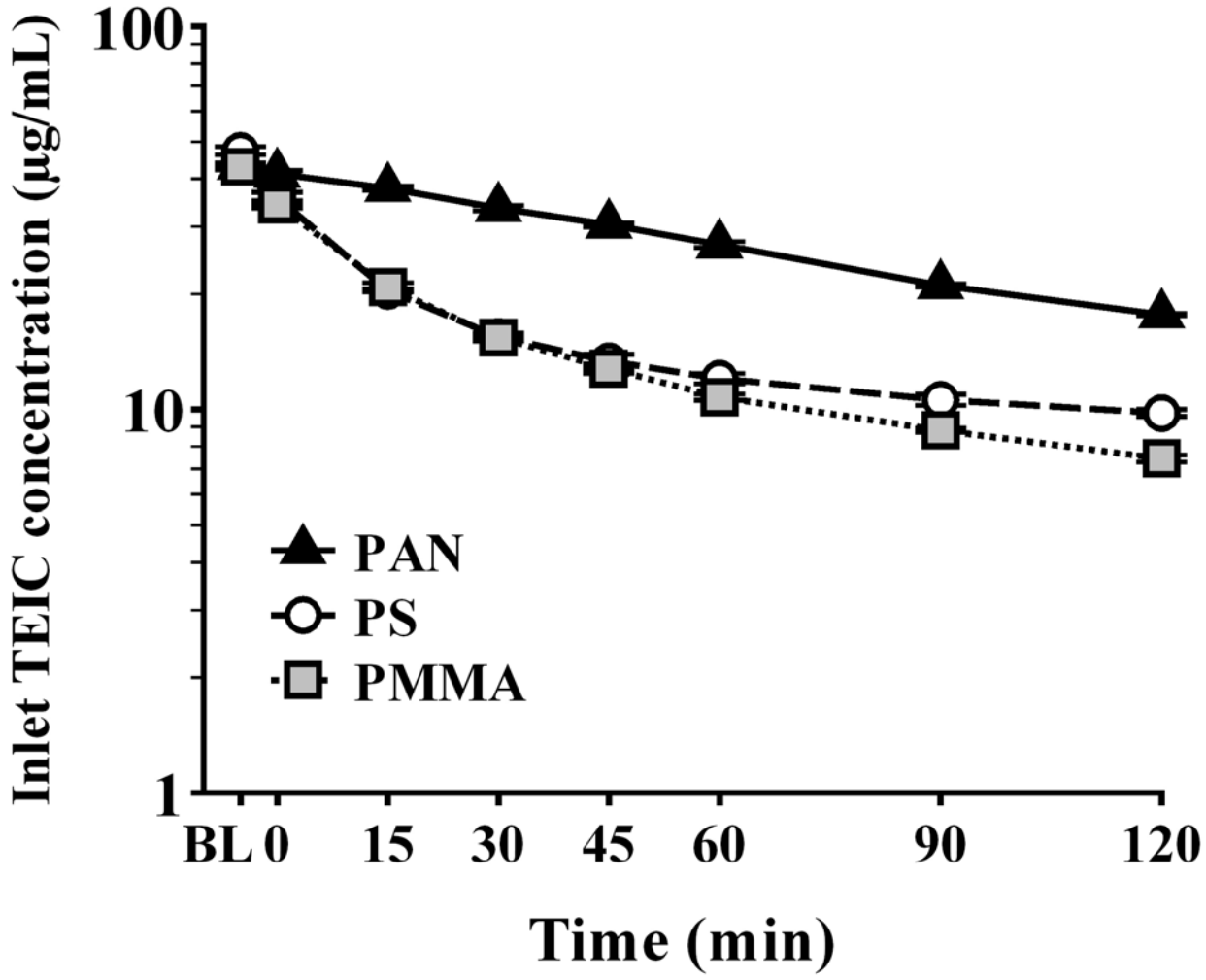

Figure 4: Changes in teicoplanin concentration at the inlet of filter membranes during *in vitro* CHDF experiment with albumin. Each symbol with vertical bar represents the mean ± S.E. (n = 3). In the two series of experiments with (shown in this figure)and without albumin (not shown), the decline of teicoplanin was significantly different among the three filter membranes (PMMA > PS > PAN, two-way repeated measures ANOVA followed by Tukey-Kramer test, $p < 0.05$).

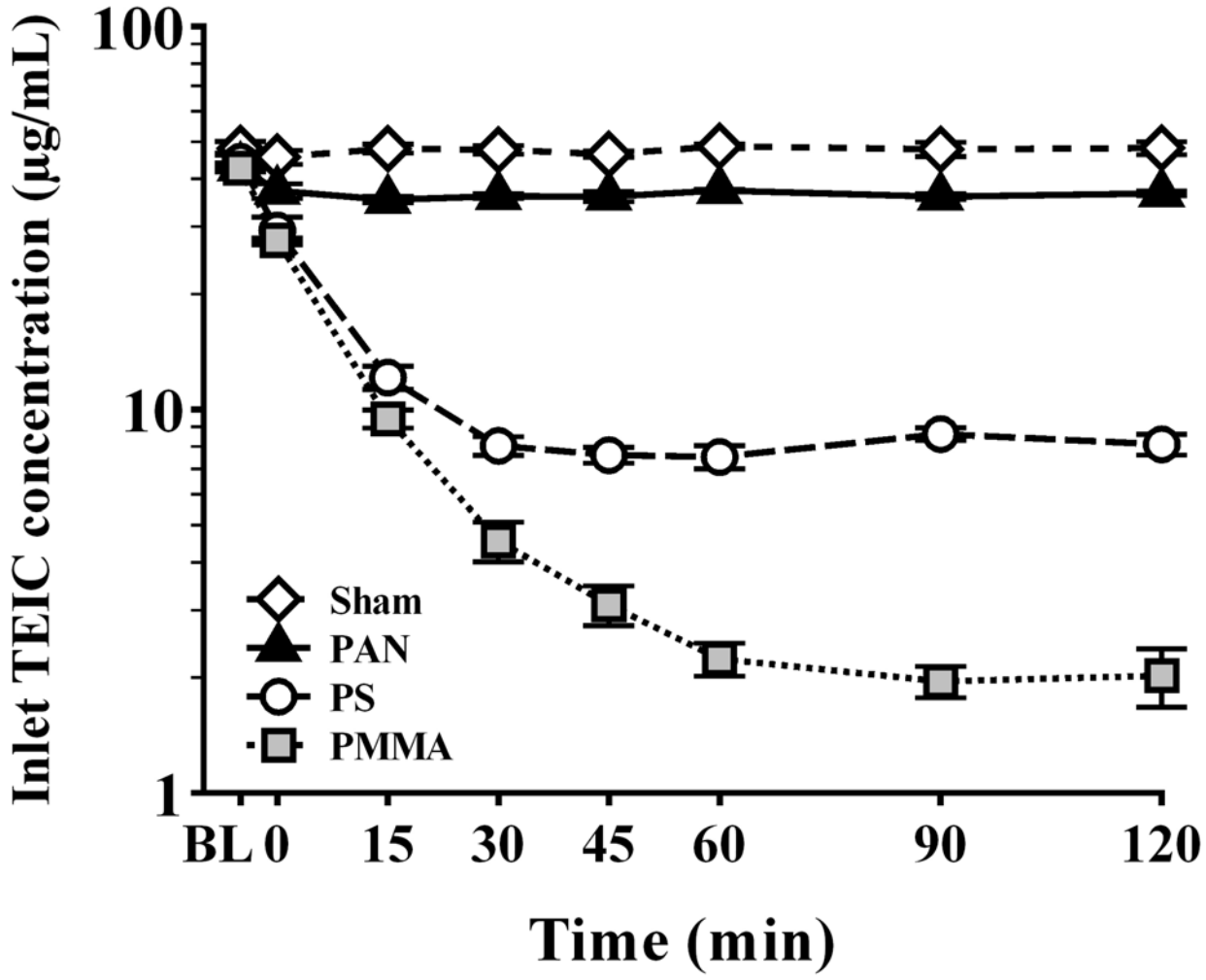

Figure 5: Changes in teicoplanin concentration at the inlet of filter membranes during a simple circulation without filtration or dialysis. Each symbol with vertical bar represents the mean ± S.E. (n = 3). The decline of teicoplanin was significantly different among the control and the three membranes. (two-way repeated measures ANOVA followed by Tukey-Kramer test, $p < 0.05$).