Renal Replacement Therapy

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In vitro effects of anti-MRSA agent adsorption onto the AN69ST hemofilter

Yoshinori Inano[1*], Kayoko Tsuchiya[1], Ryota Kumano[1], Go Miura[1] and Hiromitsu Nakasa[1,2]

Abstract

Background Blood purification therapy with a sulfonated polyacrylonitrile surface treated (AN69ST) hemofilter is used to treat sepsis. However, the AN69ST hemofilter has been reported to adsorb and remove therapeutic drugs; warranting further investigation. In this study, we evaluated the adsorption effects of AN69ST membranes and hemofilters connected to a dialysis circuit model on anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agents, such as arbekacin sulfate (ABK), linezolid (LZD), vancomycin hydrochloride (VCM), teicoplanin (TEIC), and daptomycin (DAP), in in vitro experiments.

Methods Drug solutions were exposed to AN69ST membranes. The absorbance of the drug solution was measured over time, and the drug content was calculated. Additionally, we calculated the drug content over time by circulating the drug solution through a dialysis circuit model. The clearance of each drug was determined at 5 and 60 min.

Results The content of ABK, TEIC, DAP, and VCM decreased substantially after the addition of AN69ST membranes compared to those of the standard reagent. However, the LZD content did not decrease. In the dialysis circuit model, the content of ABK, TEIC, DAP, and VCM were 3.7%, 25.7%, 43.8%, and 44.5%, respectively, at 20 min, which were clearly lower than those of the standard reagent (62–64%). However, the LZD content remained unchanged. The clearance of ABK, TEIC, DAP, and VCM increased after 5 min.

Conclusions The in vitro adsorption of anti-MRSA agents onto the AN69ST hemofilter was confirmed for ABK, TEIC, DAP, and VCM. Positively charged ABK was particularly susceptible to adsorption and should be avoided during blood purification using the AN69ST hemofilter. In addition, we concluded that TEIC, DAP, and VCM should be used for therapeutic drug monitoring because the adsorption rate of each drug is believed to vary depending on its protein binding rate.

Keywords AN69ST, Continuous hemodiafiltration, Adsorption, Arbekacin, Linezolid, Vancomycin, Teicoplanin, Daptomycin

Introduction

In 2016, the definition of sepsis was changed in Sepsis-3 to life-threatening organ dysfunction caused by a dysregulated host response to infection. This has made the use of early measures to prevent the progression of organ damage essential in the treatment of sepsis. Organ damage is believed to be characterized by pathogen-associated molecular patterns, derived from pathogenic microorganisms, and damage-associated molecular patterns. These patterns are released from the body upon infection, causing hypercytokinemia, thereby resulting

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in increased vascular permeability, circulatory failure, immunodeficiency, and various types of cell death [1]. In the field of emergency medicine, blood purification therapies, such as continuous hemodiafiltration (CHDF) using cytokine-adsorbing hemofilters (CAH), are performed to improve hypercytokinemia as a part of sepsis and septic shock treatment.

Cytokine-adsorbing hemofilters, which consist of polymethyl methacrylate and sulfonated polyacrylonitrile surface treated (AN69ST) membranes, are used to adsorb cytokines [2–4]. In particular, the AN69ST membrane is negatively charged because of its hydrogel structure, which is composed of hydrophobic acrylonitrile and hydrophilic sodium methallyl sulfonate. AN69ST membranes are reported to exhibit effective adsorption properties for positively charged cytokines [5, 6]. The adsorption properties of the AN69ST membrane have attracted considerable attention overseas, and several clinical trials using oXiris®, an improved version of the AN69ST hemofilter used in Japan, are underway [7, 8]. Additionally, in 2020, the year of the global coronavirus disease 2019 (COVID-19) pandemic, the U.S. Food and Drug Administration approved oXiris® for emergency use as a product with potential to improve hypercytokinemia caused by COVID-19 [9, 10].

However, AN69ST hemofilters have also demonstrated adsorption and removal of nafamostat mesilate (NF), an anticoagulant used during CHDF [11]. For this reason, when performing CHDF with the AN69ST hemofilter (AN69ST–CHDF), it is imperative that NF is administered in a different manner than that used in the past [12]. The AN69ST hemofilter is assumed to adsorb other therapeutic drugs, thereby producing a complication in the field.

We previously studied the effect of essential antimicrobial agent adsorption onto AN69ST membranes for sepsis treatment by removing hollow fiber membranes from hemofilters. We reported that glycopeptide agents, vancomycin hydrochloride (VCM) and teicoplanin (TEIC), which are anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agents, tend to be particularly susceptible to adsorption [13]. Anti-MRSA agents are among the most important drugs for sepsis treatment [14]. Therefore, the adsorptive removal of anti-MRSA agents by the AN69ST hemofilter can affect the life expectancy of patients and requires immediate investigation. However, to our knowledge, there are no reports on the effects of adsorption onto the AN69ST membranes for anti-MRSA agents such as arbekacin sulfate (ABK), linezolid (LZD), and daptomycin (DAP). In addition, the effect of adsorption onto the AN69ST hemofilter when anti-MRSA agents are circulated in the dialysis circuit has not been elucidated.

The purpose of this study is therefore to determine the method to ensure the efficacy of anti-MRSA agents for treatment without their adsorption and removal by the AN69ST hemofilter when performing blood purification therapy. We investigated the adsorption of anti-MRSA agents onto the AN69ST membranes and compared the adsorption based on antimicrobial classification. In addition, using a dialysis circuit model connected to the AN69ST hemofilter, effects of adsorption of anti-MRSA agents on the AN69ST hemofilter in vitro were investigated.

Materials and methods

Materials

The anti-MRSA agents used were the semisynthetic aminoglycoside ABK (Arbekacin Sulfate Injection; 25 mg; Takeda Pharma Co., Ltd., Osaka, Japan), oxazolidinone LZD (LINEZOLID for I.V. Infusion; 600 mg; neo Criti-Care Pharma Co., Ltd., Tokyo, Japan.), VCM (Vancomycin 0.5 g; Meiji Seika Pharma Co., Ltd., Tokyo, Japan), TEIC (TEICOPLANIN, intravenous for drip use; 200 mg; Fuji Pharma Co., Ltd., Tokyo, Japan), and cyclic lipopeptide DAP (CUBICIN® IV 350 mg; MSD Co., Ltd., Tokyo, Japan) (Fig. 1). To exclude the influence of molecular size, meropenem hydrate (MEPM; Meropenem for Injection; 0.25 g; Pfizer Japan Inc., Tokyo, Japan; molecular weight: 437.51) and cyanocobalamin (CN-Cbl; FUJIFILM Wako Pure Chemical Co., Osaka, Japan; molecular weight: 1355.37), which were confirmed not to be adsorbed onto the AN69ST membranes in preliminary tests and had molecular weight similar to that of the target drugs, were used as standard reagents. The AN69ST hemofilter (sepXiris ®150; Baxter Co., Ltd., Tokyo, Japan) was used. Hollow fiber membranes were removed by disassembling the housing of the hemofilter. The blood purification system (Prismaflex®; Baxter Co., Ltd., Tokyo, Japan) was used exclusively for the AN69ST hemofilter.

Concentration preparation and quantification methods

The molar concentration of each drug was diluted with a saline solution to achieve 60–80 μmol/L. Arbekacin sulfate (ABK) was prepared at a concentration of 40 μg/mL, VCM at 100 μg/mL, and TEIC and DAP at 120 μg/mL. Standard reagents were similarly set with MEPM and CN-Cbl at 25 and 100 μg/mL, respectively. Linezolid was prepared at a concentration of 25 μg/mL by dilution with 5% dextrose solution, which is the same as the product solvent.

Drug quantification was performed by measuring the absorbance at the maximum absorption wavelength of each drug (VCM: 280 nm; TEIC: 279 nm; LZD: 250 nm; and DAP: 261 nm) using a spectrophotometer (BioSpec-mini, Shimadzu Co., Kyoto, Japan). For ABK,

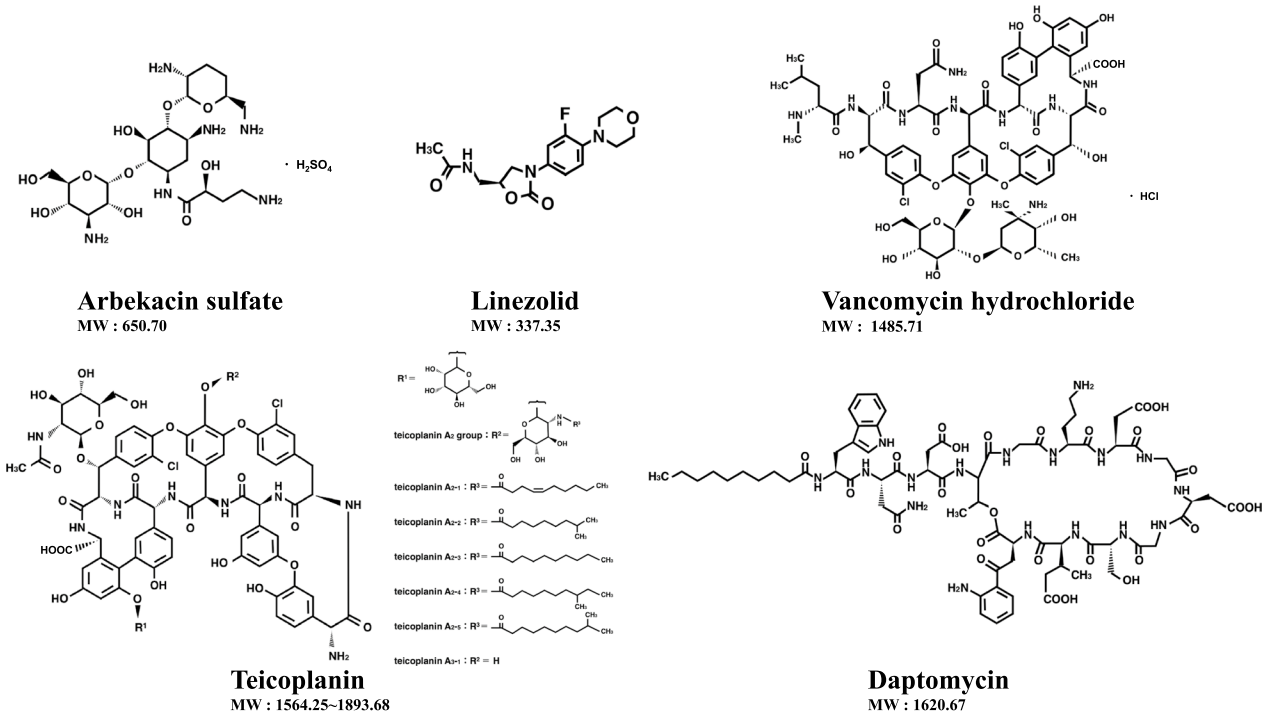

Fig. 1 Structural formulas of anti-MRSA agents. *MW* Molecular weight

trinitrophenyl derivatization using trinitrobenzenesulfonic acid sodium salt dihydrate (FUJIFILM Wako Pure Chemical Co.) was performed, and the absorbance was measured at the maximum absorption wavelength of 412 nm.

Methods

Experiment using AN69ST membranes

The AN69ST membranes (approximately 0.08 m^3 in size) were added to 200 mL of each drug solution and agitated at 37 °C (Fig. 2). The drug solution was collected before and at 1, 5, 10, 15, 20, 30, and 45 min after the addition of the AN69ST membranes, and the absorbance was measured. The drug content was calculated by determining the concentration based on the measured absorbance. Standard reagents used for ABK and LZD (molecular weight below 1000) were MEPM (hereafter called "standard-I") and for VCM, TEIC, and DAP (molecular weight above 1000) were CN-Cbl (hereafter called "standard-II"). The experiment was performed four times for each drug, and values are presented as mean ± standard deviation.

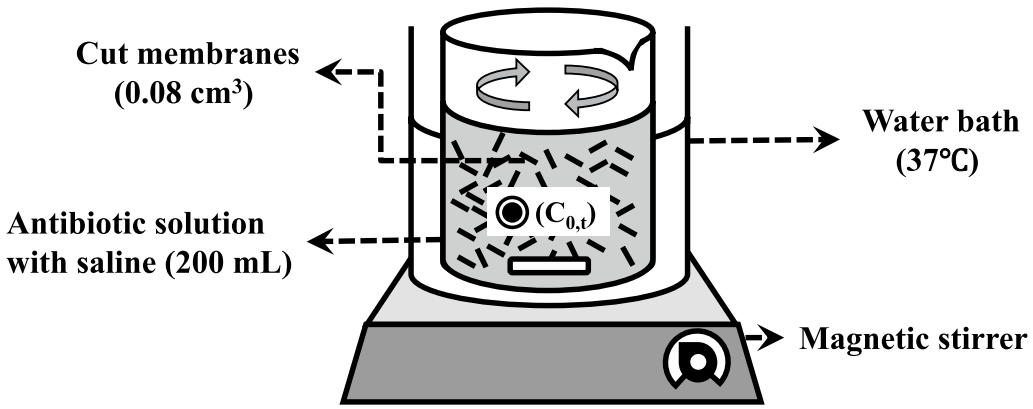

Fig. 2 Device used in an adsorption experiment performed on AN69ST membranes. Double circles indicate sampling points

Experiment using the dialysis circuit model

Priming was performed using heparin-containing saline (5000 U/L). Subsequently, a drug solution (1000 mL) was circulated at a solution flow rate (Q_B) of 80 mL/min while maintained at 37 °C. Saline was used as dialysate. The dialysate (Q_D) and filtration flow rate (Q_F) were both set at 500 mL/h to eliminate the effects of ultrafiltration (Fig. 3). Drug solutions were collected at 0 min of circulation and then, at 5, 10, 20, 30, 60, and 120 min; the absorbance was measured. The drug content was calculated by determining the concentration based on the absorbance measured. Due to the start time being defined as the time when the priming solution in the circuit was replaced by the drug solution, 0 min was set after a 150 s delay. In addition, the drug solutions were collected at 5 and 60 min at the inlet and outlet of the hemofilter, and the concentrations were measured to calculate the clearance of each drug.

Calculations

The drug concentration was calculated based on the absorbance measured using a calibration curve. Drug content was calculated using the following equation:

$$Content\ of\ drug(\%) = \frac{C_t}{C_0} \times 100$$

where C_0 is the initial concentration of the drug solution, and C_t is the concentration of the drug solution collected over time.

The clearance of each drug was calculated using the following equation:

$$Clearance\left(\frac{\mathrm{mL}}{\mathrm{min}}\right) = \frac{C_{in} - C_{out}}{C_{in}} \times QB$$

where C_{in} and C_{out} are the concentrations of the drug solutions collected at the inlet and outlet of the hemofilter, respectively, and Q_B is the solution flow rate.

Statistical analyses

To evaluate adsorption on the AN69ST membranes, Dunnett's test was performed using the multiple comparison procedure between the standard reagent and each drug. Statistical analysis was performed using RcmdrPlugin software, EZR (Easy R) [15]. $p < 0.01$ was considered statistically significant.

Results

Experiment using AN69ST membranes

The changes in the content of each drug after the addition of AN69ST membranes are shown in Fig. 4. First, we examined ABK and LZD (Fig. 4A). The ABK content

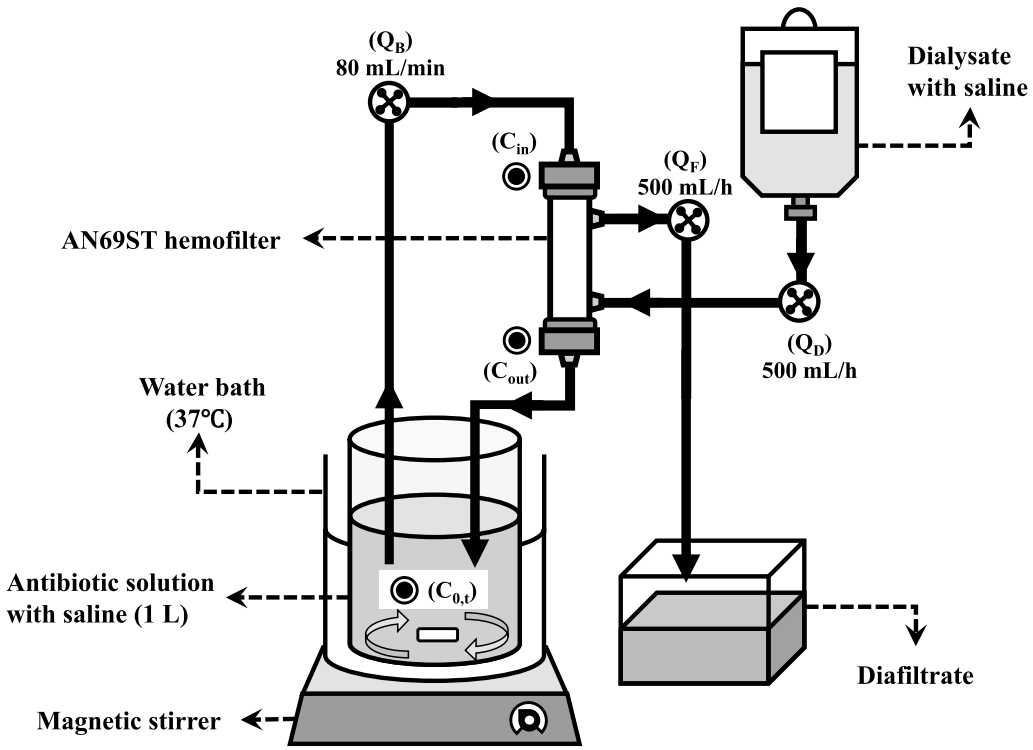

Fig. 3 In vitro dialysis circuit model device. Black arrows indicate solution flow, and double circles indicate sampling points

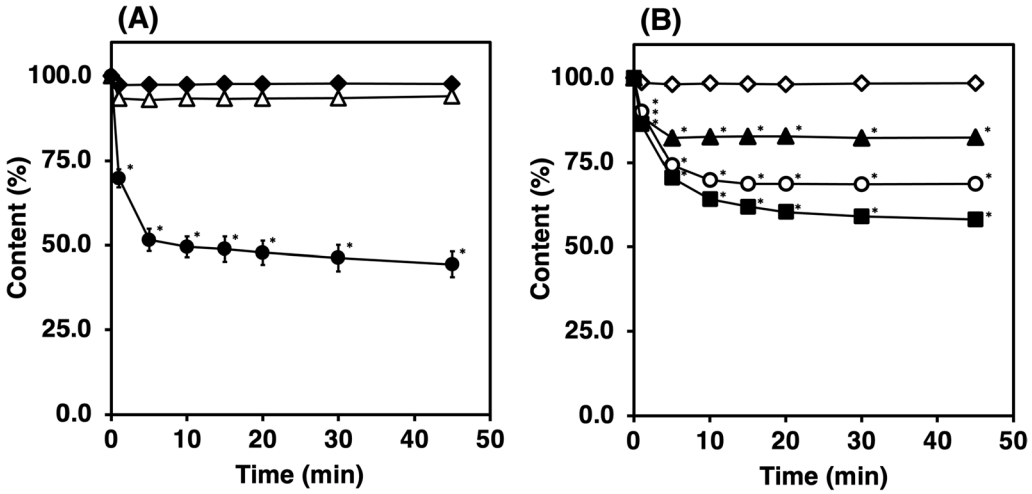

Fig. 4 Changes in the content of anti-MRSA agents after AN69ST membrane exposure. **A** Drugs with molecular weight below 1000; **B** Drugs with molecular weight over 1000. (filled circle): Arbekacin; (white triangle): Linezolid; (filled diamond): Standard-I: Meropenem; (filled triangle): Vancomycin; (white circle): Daptomycin; (filled square): Teicoplanin; (white diamond): Standard-II: Cyanocobalamin. All data are presented as mean ± SD (n = 4). *: $p < 0.01$.

decreased to 69.8% at 1 min and 51.6% at 5 min. This rapid decrease slowed down after 5 min and gradually decreased to 44.4% at 45 min. Linezolid had a slight decrease to 93.3% at 1 min but no significant changes were observed thereafter. The Dunnett's test for ABK using standard-I showed a significant difference after 1 min ($p < 0.01$), whereas LZD did not.

Next, we examined TEIC, DAP, and VCM (Fig. 4B). The content of TEIC, DAP, and VCM decreased immediately after the start and were 64.1%, 69.8%, and 82.7% at 10 min, respectively. Thereafter, however, the content of all three drugs decreased only slightly. The Dunnett's test using standard-II showed significant differences after 1 min for all three drugs ($p < 0.01$).

Experiment using the dialysis circuit model

The changes in the content of each drug after circulation in the dialysis circuit model are shown in Fig. 5. The content of all drugs decreased by approximately 20% at 0 min owing to the dilution of the priming solution in the circuit. Compared with standards I and II,

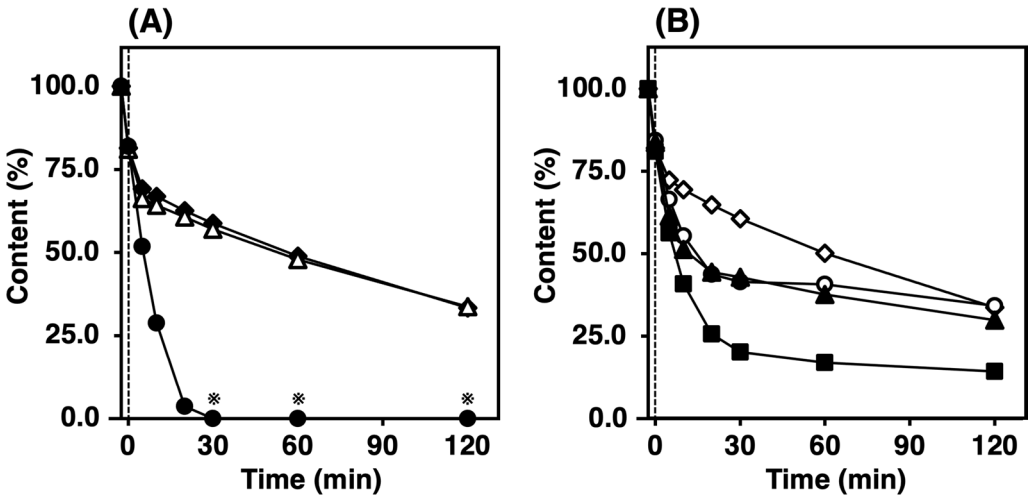

Fig. 5 Changes in the content of anti-MRSA agents in the in vitro dialysis circuit model. **A** Drugs with molecular weight below 1000; **B** Drugs with molecular weight over 1000. (filled circle): Arbekacin; (white triangle): Linezolid; (filled diamond): Standard-I: Meropenem; (filled triangle): Vancomycin; (white circle): Daptomycin; (filled square): Teicoplanin; (white diamond): Standard-II: Cyanocobalamin. ※: Unable to measure as level was below measurement limit. The start time (0 min) was set after a 150 s delay to allow the circuit to fill with the drug solution

the change in the content of ABK, TEIC, VCM, and DAP clearly decreased, whereas the LZD content was unchanged (Fig. 5).

In terms of the drug content, ABK decreased rapidly from 0 min, reaching 28.8% at 10 min, 3.7% at 20 min, and finally, decreased below the measurement limit after 30 min. In contrast, LZD had a gradual decrease to 64.2% from 0–10 min and to 60.6% at 20 min (Fig. 5A). Teicoplanin (TEIC), DAP, and VCM decreased after the start and were 25.7%, 43.8%, and 44.5% at 20 min, respectively. Thereafter, they continued to decrease gradually (Fig. 5B).

The clearance of each drug at 5 and 60 min is shown in Fig. 6. For clearance at 5 min, ABK had the highest clearance at 80 mL/min as the outlet concentration was below the measurement limit. Teicoplanin (TEIC), VCM, and DAP were 65.8, 43.8, and 38.2 mL/min, respectively, which were higher than those in standards I and II. The LZD was only 6.6 mL/min, which is similar to that of standards I and II. The clearance at 60 min was similar to that of standards I and II, with all drugs below 10 mL/min, except for ABK, which was below the measurement limits for both the inlet and outlet concentrations.

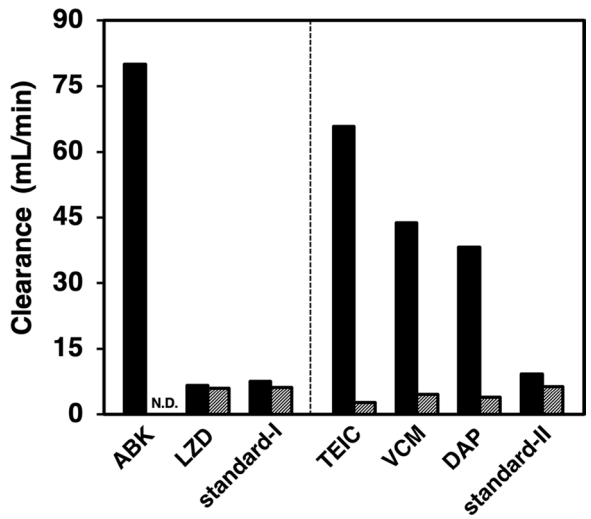

Fig. 6 Clearance of anti-MRAS agents in the in vitro dialysis circuit model. Black area indicates clearance at 5 min. Shaded area indicates clearance at 60 min. The three samples on the right had molecular weights below 1000. After the fourth stage, the samples had molecular weights greater than 1000. The clearance of ABK at 60 min could not be calculated because the inlet and outlet ABK concentrations were below the measurement limits. *ABK* Arbekacin; *LZD* Linezolid; Standard-I, Meropenem; *TEIC* Teicoplanin; *VCM* Vancomycin; *DAP* Daptomycin; Standard-II, Cyanocobalamin. *N.D.*: Not detected

Discussion

Anti-MRSA agents are essential for emergency septic treatment; however, some agents tend to be absorbed onto the AN69ST hemofilter. To date, we have examined the adsorption of two anti-MRSA agents, namely VCM and TEIC (both glycopeptide), onto AN69ST membranes [13]. In this study, we compared the effects of adsorption onto AN69ST membranes with the addition of ABK (aminoglycoside), LZD (oxazolidinone), and DAP (cyclic lipopeptide).

We investigated changes in the drug content in the presence of AN69ST membranes. The semisynthetic aminoglycoside ABK showed the highest decrease in the content among all the examined drugs and was substantially different from that of standard-I. Aminoglycoside drugs have amino groups in their structure and are positively charged in aqueous solutions [16]. The adsorption mechanism of the AN69ST membrane depends on the ionic binding of positively charged substances due to the strong negative charge of the sulfonate groups of sodium methallyl sulfonate that are a part of the membrane [6]. These results suggest that ABK, which has multiple amino groups, was more easily adsorbed by the AN69ST membranes than the other drugs, thereby resulting in the lowest content.

Conversely, the oxazolidinone drug LZD showed almost no decrease in content. Linezolid (LZD) does not have a positively charged functional group unlike ABK. Therefore, LZD was not adsorbed onto the AN69ST membranes and its content did not decrease.

Glycopeptide agents, TEIC and VCM, and the cyclic lipopeptide, DAP, were believed to be adsorbed onto AN69ST membranes because the content of all three drugs decreased substantially compared to that of standard-II. However, TEIC, VCM, and DAP did not show differences in adsorption based on the number of amino groups as was the case for ABK and LZD. Both TEIC and VCM are steric structures consisting of peptide bonds between multiple sugars and amino acids, whereas DAP is a cyclic structure consisting of multiple amino acids. It is possible that adsorption other than ionic bonding occurred because of intermolecular interactions caused by these complex molecular structures.

Standards I and II were used as the basis to analyze changes in the content. The content of standards I and II were similar and decreased gradually, regardless of the molecular weight. The principles of dialysis include diffusion, filtration, and adsorption [17]. As this study excluded the effect of ultrafiltration, the decrease in the standard content that was not adsorbed onto the AN69ST membrane can be due to the effect of diffusion. Accordingly, we assumed that the changes in the drug were the same as those of the standard drug and

therefore they were concluded to be due to diffusion, whereas changes in the drug, which were different to those of the standard drug, were assumed to be due to diffusion and adsorption. Based on this, we compared the changes in the content of each drug. Linezolid (LZD) showed changes similar to those in standards I and II, whereas ABK, TEIC, DAP, and VCM showed a clear decrease immediately after the start.

Senno et al. [18] reported that interleukin-6 clearance of the AN69ST hemofilter in patients undergoing AN69ST–CHDF was the highest at 15 min, whereas it was considerably low at 1 h. Hence, the adsorption action of the AN69ST hemofilter was considered to be effective at an early stage. The clearance of ABK, TEIC, DAP, and VCM, which decreased in content in this study, had an initial increase at 5 min then decreased at 1 h to the same levels as those of standards I and II. These results suggest that ABK, TEIC, DAP, and VCM, with the exception of LZD, decreased in content due to adsorption onto the AN69ST hemofilter.

Finally, based on this study and previous studies, we discuss the effects of adsorption and treatment of each drug when the AN69ST hemofilter is used in blood purification therapy.

In this study, LZD showed almost no adsorption onto the AN69ST hemofilter. Hiraiwa et al. [19] also reported that LZD added to a buffer solution containing fetal bovine serum and circulated in closed-circuit circulation using an AN69ST hemofilter did not show enough adsorption to affect therapy. Furthermore, Yamashina et al. [20] reported that the CHDF clearance of LZD in patients receiving AN69ST–CHDF did not increase rapidly and that effective blood concentrations were maintained. Therefore, we concluded that LZD can be administered without factoring in adsorption removal by the AN69ST hemofilter.

To our knowledge, no previous studies have discussed the adsorption of ABK on the AN69ST hemofilter. However, Urata et al. [21] reported that the AN69 membrane, which was the basis for the development of the AN69ST membrane, substantially increased the dialysis clearance of patients on ABK for up to 2 h after the start of dialysis. AN69 membrane, developed in 1969, is synthetic polymer membrane with highly hydrophilic and charged properties [5, 22]. Although these membranes are highly useful such as adsorbing cytokines, they also have the problem that bradykinin is produced when the membrane surface comes into contact with blood. In response, the surface of AN 69 membrane was treated with polyethyleneimine to develop the AN69ST membrane. Incidentally, these surface treatments have no effect on the adsorption capacity of cytokines. In this study, the adsorption capacity of the AN69ST hemofilter for ABK was extremely high, similar to that reported with the AN69 hemofilter [21]. Therefore, ABK was expected to affect the treatment because of its adsorption onto the AN69ST hemofilter; hence, other drugs should be considered for treatment.

Sawada et al. [23] reported that when TEIC was added to a buffer solution containing human serum albumin and circulated in the AN69ST–CHDF model, the clearance of TEIC fluctuated, contributing to diafiltration, and the effect of adsorption was negligible. However, our results show that TEIC was second to ABK in terms of adsorption. A possible explanation for this could be that the protein binding of TEIC is involved. Nakanishi et al. [24] reported that the adsorption performance of AN69 membranes on drugs decreased based on the protein binding potential of the drugs. Although the protein binding rate of TEIC is over 90% [25], we examined the interaction between the membrane and the drug without the addition of serum proteins. Hence, we presume that TEIC was adsorbed in this study because it was present as a free drug. For clinical use, TEIC mostly binds to albumin in the blood. Therefore, the dosage regimen for TEIC should be based on that reported by Sawada et al. [23]. However, if a patient is hypoalbuminemic, adsorption to the AN69ST hemofilter should be considered because of the increased percentage of free drugs.

Uchida et al. [26] reported the clearance of VCM when added to a buffer solution containing human serum albumin and circulated in the AN69ST–CHDF model. The clearance of VCM increased temporarily due to adsorption until 10 min into the process but decreased thereafter, with fluctuations contributing to diafiltration. These results are similar to those of our study. Accordingly, we concluded that the adsorption of VCM by the AN69ST hemofilter was affected only by the initial dose; however, this effect was attenuated by maintenance dosing.

To our knowledge, no previous studies have discussed DAP adsorption onto the AN69ST hemofilter. The changes in the DAP content in the dialysis circuit model were almost consistent with those in the VCM content assessment, which was inferred to be relatively unaffected by adsorption. In addition, the protein binding rate of the drug is as high as 90–93% for DAP [27] compared to 30–37% for VCM [28]. Based on these findings, the effect of DAP adsorption onto the AN69ST hemofilter was expected to be less than that of VCM.

Since the release of the AN69ST hemofilter in 2014, there have been few studies on the dialyzability of anti-MRSA agents with the AN69ST hemofilter. Although this study was useful in predicting clinical efficacy, it also had several limitations. First, the sample size was small. The study using the dialysis circuit model was a single study. We will need to increase the number of samples

to confirm the reproducibility of the study. Second, there was no albumin or other protein added, and the protein binding was not anticipated. Since the drug adsorption onto the AN69ST hemofilter is affected by protein binding, future studies are necessary to take protein binding into account. Finally, this study was an in vitro study that differed in many respects from clinical conditions. Therefore, at this time, we believe that therapeutic drug monitoring and dose design based on previous studies are important to ensure the efficacy of anti-MRSA drugs when performing blood purification therapy using an AN69ST hemofilter. In the future, we consider it important to accumulate clinical evidence as well as research on these issues.

Conclusions

The in vitro adsorption of anti-MRSA agents onto the AN69ST hemofilter was confirmed for ABK, TEIC, DAP, and VCM but not for LZD. In particular, the positively charged ABK was the most affected by adsorption. Therefore, ABK administration should be avoided when performing blood purification therapy using the AN69ST hemofilter. In addition, we concluded that therapeutic drug monitoring is preferable when TEIC, DAP, and VCM are administered because the adsorption of these drugs is likely to vary depending on the protein binding rate of each drug.

Abbreviations

ABK	Arbekacin
AN69	Sulfonated polyacrylonitrile
AN69ST	AN69 surface treated
CAH	Cytokine-absorbing hemofilter
CHDF	Continuous hemodiafiltration
CN-Cbl	Cyanocobalamin
COVID-19	Coronavirus disease 2019
DAP	Daptomycin
LZD	Linezolid
MEPM	Meropenem
MRSA	Methicillin-resistant *Staphylococcus aureus*
NF	Nafamostat mesilate
TEIC	Teicoplanin
VCM	Vancomycin

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Not applicable.

Author contributions

YI designed the study, performed the experiments, analyzed the data analyses, and wrote the manuscript. KT and RK performed the experiments and analyzed the data. GM and HN participated in the study design and contributed to the study concept. All the authors have read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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