In vitro Evaluation of Linezolid and Doripenem Clearance with Different Hemofilters

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Keywords

Experimental model · Adsorption · Hemofilter · Linezolid · Doripenem

Abstract

Introduction: Renal replacement therapy (RRT) is widely used in the treatment of septic acute kidney injury. However, little is known about how the adsorption properties of hemofilters used in RRT affect antibiotic concentration. Because a cytokine-adsorption membrane is frequently used in RRT, it is important to determine the antibiotic adsorption capacity of this membrane. **Objective:** The present study aimed to investigate the antibiotic adsorption capacity of different hemofilter membranes by in vitro experiments using 2 antibacterial agents (linezolid and doripenem). **Methods:** We performed experimental hemofiltration in vitro using polyacrylonitrile (AN69ST), polymethylmethacrylate (PMMA), and polysulfone (PS) hemofilters for 1,440 min. The

test solution was a 1,000-mL substitution fluid containing 30 µg/mL linezolid and 120 µg/mL doripenem. We measured drug concentrations at the inlet, outlet, and filtrate ports of the hemofilters for 1,440 min and calculated the sieving coefficient (SC) and adsorption rate (Ra) of the drugs onto the hemofilters. **Results:** The amount of linezolid adsorbed onto AN69ST, PMMA, and PS membranes was decreased relative to that in the control group at 15 min ($p < 0.05$). However, no SC for linezolid was obtained thereafter. The Ra of linezolid onto AN69ST, PMMA, and PS membranes was higher than that in the control group ($p < 0.05$). In contrast, no significant differences were observed in the concentrations and Ra values of doripenem adsorbed onto AN69ST, PMMA, and PS membranes compared with those in the control group. **Conclusions:** Doripenem was not adsorbed onto PMMA, PS, and AN69ST membranes. Linezolid was adsorbed onto PMMA, PS, and AN69ST membranes, but only temporarily, and this did not affect drug bioavailability.

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Introduction

Sepsis is the primary cause of acute kidney injury (AKI) in intensive care units (ICUs), accounting for half of all AKI cases [1, 2]. Management of septic AKI is based on early resuscitation and timely administration of appropriate antibiotics. Although renal replacement therapy (RRT) offers hemodynamic and metabolic stability and fluid balance, there are increasing concerns about its impact on antimicrobial treatment. Linezolid and doripenem are antibiotics that are commonly used against resistant bacteria in ICUs [3, 4]. Linezolid is efficacious against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci, and therefore frequently used in ICU patients [3, 5]. The most common linezolid-dosing regimen is 300 mL infusion bag (600 mg) every 12 h. Linezolid is often administered, in combination with RRT because of the daily infusion load of 600 mL, but its reported side effect include thrombocytopenia during renal dysfunction has been reported. Although Carbapenems are not first line of antibiotics in ICUs, they are frequently used in critically ill patients. Especially in severe sepsis and septic shock are major causes of morbidity and mortality in the ICUs, applicable international guidelines early recommend the early use of carbapenems as empirical therapy [5]. Owing to their hydrophilicity, they are readily removed by hemofilters during RRT for septic AKI [6, 7]. Appropriate antibiotic therapy during RRT is critical because it affects both the patients' prognosis and the emergence of resistant bacteria. Antibiotic dosing in RRT is complex, and current approaches are imprecise. Antibiotic elimination is influenced by patient and drug factors and various aspects of RRT technique, such as filtration and dialysis [8, 9]. However, little is known about how the adsorption properties of hemofilters used in RRT affect antibiotic concentrations in patients.

In Japan, cytokine-adsorbing hemofilters are frequently used in RRT. Adsorption of antibiotics onto these filters is an important consideration because it can affect treatment. In this study, we investigated potential changes in linezolid and doripenem dosage caused by their adsorption onto hemofilters by performing in vitro experiments using 3 types of hemofilters.

Materials and Methods

Preparation of Solution

The test solution was prepared by dissolving 35 g of fetal bovine serum (FBS; MW 66.5 kDa; Wako Pure Chemical, Osaka, Japan) in

Fig. 1. Schematic representation of closed-circuit circulation. The parameters of the experimental circuit (CBi, CBo, and CF) were measured as indicated according to the procedure used in clinical application.

1,000 mL of bicarbonate Ringer's solution (BICANATE Injection®; Otsuka Pharmaceutical Factory, Tokushima, Japan). We adopted a closed circulation circuit and prepared linezolid and doripenem as the target drugs, and the concentrations were adjusted to 30 and 120 µg/mL, respectively, by dissolving in 1,000 mL FBS.

Hemofiltration Procedure

Filtration of the test solution was initiated at a temperature of 37°C and using a magnetic stirrer to ensure uniform drug concentration throughout the circuit. The test solution was pumped from the solution reservoir to the hemofilter at a solution flow rate of 100 mL/min and a filtrate flow rate of 1,000 mL/h. Experimental hemofiltration was conducted for 1,440 min using a fully automated instrument (TR525®; Toray industries, Tokyo, Japan; Fig. 1).

We used the following 3 types of hemofilters – each with a surface area of 1.0 m² (Table 1) – that are used in clinical practice: polyacrylonitrile (AN69ST) hemofilter (AN69ST; Baxter Limited, Tokyo, Japan), polymethylmethacrylate (PMMA) hemofilter (Hemofeel®CH-1.0N; Toray Industries Co., Ltd., Tokyo, Japan), and polysulfone (PS) hemofilter (Excel Flow®; Asahi Kasei Medical Co., Ltd., Tokyo, Japan).

In the control group, ultrafiltration was performed using only the circuit without any membrane. The filter and an extracorporeal circuit were primed with 1,000 mL of heparinized saline solution (5,000 IU).

Sampling Method and Evaluation Parameters

Circulation was carried out for 3 min to maintain a constant antimicrobial concentration in the reservoir and FBS circuit. The time after circulation for 3 min was set as time 0. Experimental

Table 1. Characteristics of the different hemofilters tested in this study

	Material	Structure	Surface area, m ²	SC alb, %	Inner diameter, μm	Wall thickness, μm
AN69ST	AN69ST (surface treated)	Symmetric	1.05	<0.1	210	42
CH – 1.0 N	PMMA	Symmetric	1.0	0.7	200	30
Excel flow	PS	Asymmetric	1.0	<0.1	225	45

SC, sieving coefficient; AN69ST, polyacrylonitrile; PMMA, polymethylmethacrylate; PS, polysulfone.

Fig. 2. Sampling timing for laboratory analysis. The concentrations of linezolid and doripenem from the inlet, outlet, and filtrate ports at different sampling points are shown. The circuit for 3 min and filled with solution and starting the experiment.

hemofiltration was performed for 1,440 min at 37°C, and samples for analysis of antibiotic concentration were collected from both the inlet and outlet of the hemofilter and from the filtrate port at different time points (Fig. 2). Linezolid and doripenem concentrations in the samples obtained from the inlet, outlet, and filtrate ports in the control group and in the AN69ST, PMMA, and PS membrane groups were measured by high-performance liquid chromatography (HPLC).

Plasma linezolid level was quantified by HPLC as previously reported [10], with some modifications. The sample was deproteinized by adding acetonitrile, vortexed for 30 s, and centrifuged at 3,000 rpm for 10 min. The supernatant (20 μL) was analyzed on an HPLC system consisting of LC-20AT solvent delivery pumps, and an SPD-10Avp detector (Shimadzu, Kyoto, Japan). The analytes were separated on a InertSustain®C18 column (4.6 mm, inner diameter = 150 mm; GL Sciences, Tokyo, Japan). The mobile phase consisted of 1% ortho-phosphoric acid, 30% methanol, and 2 g/L heptane sulfonic acid adjusted to pH 5.0. The flow rate was 1.0 mL/min, and linezolid was detected at 254 nm.

The retention time of linezolid was 10.0 min, and the lower limit of detection was 0.1 μg/mL. The intra- and inter-day variations of linezolid concentration measurements were <5% in this assay.

Doripenem concentration was measured with the meropenem assay as previously reported [11], with some modification. After deproteinizing 100 μL of the sample by adding 300 μL of methanol, the sample was centrifuged at 3,000 rpm for 10 min, and 30 μL of the supernatant was injected into an HPLC system consisting of a liquid

transport unit (LC-20AB; Shimadzu) and a spectrophotometer (SPD-20A; Shimadzu). The mobile phase was a mixture of PIC-A reagent/methanol (82:18), the flow rate was 1.0 mL/min, the detection wavelength was 300 nm, and a HYPERSIL, ODS-5 column was used (4.6 mm, inner diameter = 250 mm; Chemco Scientific, Osaka, Japan). The retention time of doripenem was 7.7 min, and the lower limit of detection was 0.1 μg/mL. The intra- and inter-day variations in doripenem concentration measured with this assay were <5%.

Validation of these measurement methods was performed based on the Guideline on Bioanalytical Method Validation in Pharmaceutical Development [12].

Sieving coefficient (SC) was calculated using the following equation:

$$SC = 2CF/CBi + CBo$$

where C_{Bi}, C_{Bo}, and CF are the linezolid and doripenem concentrations in the test solution at the inlet, outlet, and filtrate ports, respectively, of the hemofilter.

The amount of drug adsorbed onto the membranes was assayed at 0, 15, 30, 45, 60, 90, 120, 360, and 1,440 min. Adsorption rate (Ra) was calculated using the following equation:

$$Ra = ([\text{time 0 concentration} - \text{time 1,440 min concentration}] / \text{time 0 concentration}) \times 100\%$$

Adsorption of antibacterial agents onto hemofilters was evaluated based on Ra value.

Statistical Analysis

The results are expressed as mean values ± SD. Differences in adsorption of antibiotics onto AN69ST, PMMA, and PS membranes compared to that in the control group (*n* = 4 per group) were evaluated by one-way analysis of variance using the JMP software for SAS (SAS Institute, Cary, NC, USA). *p* < 0.05 was considered statistically significant.

Results

Concentration, SC, and Ra of Linezolid

Time Course of Linezolid Concentration

The amount of linezolid adsorbed onto the 3 membranes decreased at 15 min and remained constant until 1,440 min.

Table 2. Adsorption rate of antibiotics onto AN69ST, PMMA, and PS membranes

	Ra				<i>p</i> value
	AN69ST	PMMA	PS	Control	
Linezolid, %	11.4±1.9	22.0±1.1	14.5±3.7	1.7±1.2	<0.01*
Doripenem, %	24.0±2.5	25.5±1.8	27.7±2.5	23.5±2.5	0.06

* $p < 0.05$ vs. the control group (analysis of variance).

Adsorption rates of linezolid (30 µg/mL) and doripenem (120 µg/mL) are shown as mean ± SD of 4 experiments.

Ra, adsorption rate; AN69ST, polyacrylonitrile; PMMA, polymethylmethacrylate; PS, polysulfone.

The concentration of linezolid adsorbed onto the membranes decreased significantly from 0 to 15 min relative to that in the control group (AN69ST: 29.0 ± 0.2 to 27.9 ± 0.6 µg/mL; PMMA: 28.8 ± 0.6 to 23.6 ± 1.0 µg/mL; PS: 27.1 ± 0.5 to 26.6 ± 0.8 ; control: 29.4 ± 0.7 to 29.1 ± 1.0 µg/mL; $p < 0.05$). No significant changes were observed in the linezolid concentrations absorbed among the 3 membranes after 15 min (Fig. 3).

SC of Linezolid

The linezolid SC of AN69ST, PMMA, and PS membranes was 0.85 ± 0.01 , 0.86 ± 0.02 , and 0.85 ± 0.03 , respectively, with no significant differences observed at 1,440 min among the 3 types of membrane.

Ra of Linezolid

The Ra values for linezolid adsorption onto AN69ST, PMMA, and PS membranes were 6.6 ± 2.2 , 17.7 ± 1.5 , and $10.3 \pm 1.8\%$, respectively; these values were higher than the Ra for linezolid in the control group ($1.20 \pm 1.5\%$; $p < 0.05$; Table 2).

Concentration, SC, and Ra of Doripenem

Time Course of Doripenem Concentration

The concentration of doripenem adsorbed onto the membranes decreased from 0 to 1,440 min relative to that in the control group (AN69ST: 94.5 ± 3.1 to 72.0 ± 2.7 µg/mL; PMMA: 91.7 ± 1.7 to 69.8 ± 2.0 µg/mL; PS: 94.2 ± 2.9 to 70.9 ± 2.8 µg/mL; control: 92.5 ± 3.8 to 72.0 ± 2.5 µg/mL). None of these decreases were statistically significant compared with the control group (Fig. 4).

SC of Doripenem

The doripenem SC of AN69ST, PMMA, and PS membranes were 0.90 ± 0.09 , 0.92 ± 0.09 and 0.95 ± 0.05 , re-

Fig. 3. Linezolid concentration from the hemofilter inlet during hemodialysis. Results are shown as mean ± SD of 4 experiments. * $p < 0.05$ versus the control group (analysis of variance). ** $p < 0.05$ versus the control group (analysis of variance). *** $p < 0.05$ versus the control group (analysis of variance). AN69ST, polyacrylonitrile; PMMA, polymethylmethacrylate; PS, polysulfone.

spectively, with no significant differences observed at 1,440 min among the 3 types of membranes.

Ra of Doripenem

The Ra values for doripenem adsorption onto AN69ST, PMMA, and PS membranes at 1,440 min were 24.0 ± 2.5 , 25.5 ± 1.8 , and $27.7 \pm 2.3\%$, respectively; these values were comparable to the Ra for doripenem in the control group ($23.5 \pm 2.5\%$), and there were no differences in Ra values among the 3 types of membrane (Table 2).

Fig. 4. Doripenem concentration from the inlet during hemodialysis. Results are shown as mean $\pm$ SD of 4 experiments. AN69ST, polyacrylonitrile; PMMA, polymethylmethacrylate; PS, polysulfone.

Discussion

In this study, we performed *in vitro* experiments to evaluate the adsorption of linezolid and doripenem onto 3 different hemofilters. PMMA and AN69ST membranes, which are among the most frequently used hemofilters in RRT in Japan, have a symmetrical structure and exhibit high protein adsorption.

Other types of membranes, such as PS, polyarylethersulfone, and polyethersulfone, have an asymmetrical structure, and their separating layer is thin and located near the inner surface. In this study, we compared the antibiotic adsorption properties of PMMA, AN69ST, and PS membranes. The PMMA membrane matrix has a symmetric microporous structure that efficiently traps circulating proinflammatory cytokines used in RRT [13, 14]. AN69ST is a copolymer of hydrophobic acrylonitrile and hydrophilic sodium methallyl sulfonate and has a symmetric hydrogel structure [15]. The surface groups derived from methallyl sulfonate monomers confer a negative charge to the membrane, allowing adsorption of cytokines via ionic bonding between the sulfonate groups and the amino groups on the cytokine surface [16, 17]. Thus, cytokine-adsorbing hemofilters, such as PMMA and AN69ST, exhibit higher cytokine removal efficiency than does a PS membrane hemofilter.

Adsorption of linezolid onto AN69ST, PMMA, and PS membranes reached an equilibrium at 15 min and no further adsorption was observed thereafter. In contrast, the concentration of doripenem adsorbed onto AN69ST, PMMA, and PS membranes and in the control group decreased at a constant rate from 0 to 1,440 min.

The doripenem SC of AN69ST, PMMA, and PS membranes were 0.90 ± 0.09 , 0.92 ± 0.09 and 0.95 ± 0.05 , respectively. Since the protein nonbinding rate of doripenem is 0.91, a calculated SC value of 0.91 represents the free doripenem filtered without being adsorbed on membranes [18]. Our results were similar, suggesting that doripenem was not adsorbed on AN69ST, PMMA, or PS membranes [6].

Antimicrobial drugs, such as amikacin and teicoplanin, exhibit a high Ra (60–80%) onto PMMA and AN69 membranes *in vitro* [19, 20]. However, these reports did not mention the effect of adsorption on the bioavailability of the drugs.

Linezolid is a hydrophilic antibiotic that has a low molecular weight (337 Da), is 31% protein binding, and has a distribution volume (Vd) of 0.79 L/kg. When linezolid is administered at a dose of 600 mg to an adult patient with a body weight of 60 kg, the blood concentration is 12.7 µg/mL ($600 \text{ mg} / 0.79 \text{ L/kg} \times 60 \text{ kg}$). The concentration of free linezolid is 8.6 µg/mL ($12.7 \text{ µg/mL} \times [1 - 0.31]$).

In our study, the concentration of linezolid adsorbed onto PMMA membrane, which showed the maximum adsorption among the 3 hemofilters, was transiently decreased by 22.0% at 15 min and was stable up to 1,440 min.

In this case, the amount of linezolid adsorbed onto PMMA membrane was calculated to be 1.9 mg ($8.6 \text{ µg/mL} \times 0.22 \times 1,000 \text{ mL}$). Based on this value, the ratio of the adsorbed amount of the administered dose was estimated to be approximately 0.3% ($1.9/600$). The clearance rate of free linezolid was 16.7 mL/min even with a non-adsorbing hemofilter, when the filtration flow rate was 1,000 mL/h (16.7 mL/min); the elimination velocity of free linezolid with a non-adsorbing hemofilter was calculated to be 144 µg/min, (i.e., 207 mg/1,440 min). Thus, the adsorbed amount of linezolid (1.9 mg) was not expected to affect treatment. Earlier reports indicated that polyacrylonitrile membranes removed 8% of the antibiotic dose, but investigators believed that a dosage change was not warranted because therapeutic serum concentrations were maintained in patients [21]. In our experiment, the effect of the Ra of 0.3% was considered to be small. Furthermore, according to a recent book on critical care nephrology by Ferrari et al. [22], membrane adsorption has

probably a minor effect on drug removal. However, because dosing adjustment will not account for adsorption effects, drug-adsorbing membranes are usually not recommended for RRT [22].

Doripenem, a carbapenem antibiotic, often used to treat infections by Gram-negative bacteria that are resistant to most antibiotics, is hydrophilic, and it exhibits predominantly renal clearance. It has a low molecular weight (439 Da), is only 9% protein binding, and has a Vd ranging from 0.2 to 0.3 L/kg.

The low stability of carbapenem drugs is widely reported in the literature [23, 24]. In our in vitro experiments, doripenem degradation was observed in all solutions, including in the control group. After 1,440 min, the residual ratio was 70–80%. Moreover, there were no differences between the amounts of doripenem adsorbed onto AN69ST, PMMA, and PS membranes and that in the control group, indicating that there was no drug adsorption by the membranes.

Blood pressure is reduced owing to a decrease in circulating plasma volume, causing a large amount of infusion to be distributed to the stroma interstitium. Linezolid and doripenem have large Vd and are thus widely distributed in the interstitium and in cells. Because drug concentration in blood is lower than that in the body, drug adsorption onto hemofilters in continuous RRT has a negligible effect on drug bioavailability [25, 26]. In septic shock, an increase in interstitial fluid markedly increases the Vd of hydrophilic antibiotics and further decreases their blood concentration by dilution [26–28]. In the present study, we found that adsorption of linezolid and doripenem onto AN69ST, PMMA, and PS membranes did not affect the used antibiotics dose.

This study had several limitations. First, FBS was used as the test solution. Although whole blood is preferable for estimating drug concentration in vivo, a simple FBS solution is suitable for investigating drug adsorption onto a membrane. Second, linezolid and doripenem were added only once to the test solution; additional experiments in which the drugs are added repeatedly are needed to confirm whether further adsorption occurs. Third, we estimated the amount of drug adsorbed onto the PMMA membrane; however, because this value did not exceed the estimated amount, a more detailed examination is warranted. Finally, the synthetic protease inhibitor nafamostat mesylate is used as an anticoagulant in RRT in Japan. However, because protease activity can affect drug metabolism, nafamostat mesylate can increase the blood concentration of linezolid [29], which was not investigated in our study.

The results of our in vitro experiments revealed that adsorption of antimicrobial drugs onto hemofilters in RRT did not affect drug bioavailability. However, if the filtration volume was constant, the adsorption capacity of the membrane would majorly affect the drug dose. Adsorption of linezolid onto PMMA, PS, and AN69ST membranes was observed, but this was temporary and did not affect the drug dosage. Thus, various hemofilters can be used in RRT without them affecting antibiotic dosing.

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Statement of Ethics

The in vitro study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.H.: designed the concept and created a manuscript. K. Moriyama, K. Matsumoto, Y.S., K. Morita, and O.N.: gave ethical approval and collected data. Y.K., C.Y., Y.H., J.S., and H.K.: reviewed the policies of the existing journals. T.K., Y.K., T.N., and N.K.: contributed to the writing of the final version. All the authors have approved the final version of the manuscript.

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