LAB/IN VITRO RESEARCH

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Membrane-Dependent Adsorption of Lacosamide in CRRT: Implications for Drug Dosing in Critically Ill Renal Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Krzysztof Nosek
ACDEF 2 Milena Samiec
ABCDEF 3 Hubert Ziółkowski
ABCDEF 4 Robert Maksymowicz
ABCDEF 5 Wojciech Matuszewski
ADE 2 Dariusz Onichimowski
BCDF 3 Paulina Markowska-Buńka
ACEF 6 Krzysztof Czaja

1 Department of Pharmacology and Toxicology, Faculty of Medicine, University of Warmia and Mazury, Olsztyn, Poland
2 Department of Anesthesiology and Intensive Therapy, School of Medicine, University of Warmia and Mazury, Olsztyn, Poland
3 Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Warmia and Mazury, Olsztyn, Poland
4 Department of Human Physiology and Pathophysiology, School of Medicine, University of Warmia and Mazury, Olsztyn, Poland
5 Clinic of Endocrinology, Diabetology and Internal Medicine, School of Medicine, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland
6 Department of Biomedical Sciences, School of Veterinary Medicine, Ross University, Basseterre, St. Kitts and Nevis, West Indies

Corresponding Author: Krzysztof Czaja, Department of Biomedical Sciences, School of Veterinary Medicine, Ross University, P.O. Box 334, Basseterre, St. Kitts, West Indies, Phone: +1 5095927954, e-mail: kczaja@rosvet.edu.kn

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Background: Lacosamide is an antiepileptic drug widely used to treat partial-onset seizures. During extracorporeal therapies or intravenous administration, lacosamide adsorption to filtration membranes and its stability in solutions may influence therapeutic efficacy. This in vitro study evaluated lacosamide adsorption to different dialysis filter membranes in saline and plasma solutions, as well as its stability in these solutions.

Material/Methods: Lacosamide (200 µg/mL) was prepared in 0.9% NaCl and bovine plasma, then perfused through 3 types of dialysis filters: polysulfone (PS), polyacrylonitrile (PAN), and polyacrylonitrile polyethyleneimine (PAN-PEI). Samples were collected at 0, 5, 15, 30, 45, 60, and 90 minutes. Lacosamide concentrations were measured using high-performance liquid chromatography. Repeated-measures analysis of variance and post hoc tests were used to evaluate concentration changes over time among filter types.

Results: Lacosamide remained stable in saline and plasma solutions over 90 minutes, showing under 7% variation in concentration. In 0.9% NaCl, significant adsorption occurred across all filters, with total reductions of 14.73% for PAN-PEI, 20.71% for PAN, and 33.52% for PS filters at 90 minutes. In plasma, adsorption was lower for PS filters (17.96%) but greater for PAN-PEI (23.04%) and PAN (27.71%) filters. No significant differences in adsorption were detected among filters ($P > 0.05$).

Conclusions: Lacosamide demonstrated chemical stability with measurable adsorption to dialysis membranes. Adsorption was more pronounced in plasma than in saline for PAN-PEI and PAN membranes. These findings indicate that lacosamide concentrations may decrease during extracorporeal circulation and should be considered in settings involving hemodialysis or continuous renal replacement therapy.

Keywords: Antidepressive Agents • Calcium-Transporting ATPases • Data Science • Hydrogen Peroxide • Nephrons

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Introduction

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a third-generation antiepileptic drug discovered in 1996 at the University of Houston as a D-serine analog [1,2]. It was approved by the European Medicines Agency and the United States Food and Drug Administration in 2008 for the treatment of partial-onset seizures as monotherapy or adjunctive therapy in adults, adolescents, and children aged 4 years and older [3,4]. In addition to focal epilepsy, lacosamide has shown clinical utility in generalized tonic-clonic seizures associated with idiopathic generalized epilepsy, nonconvulsive and refractory status epilepticus, and sleep-related hypermotor epilepsy [5,6].

Lacosamide's mechanism of action is distinct from that of other sodium channel modulators. It selectively enhances the slow inactivation of voltage-gated sodium channels, stabilizing hyperexcitable neuronal membranes without substantially affecting the fast inactivation mechanism shared by older antiepileptic drugs such as phenytoin and carbamazepine [1,7]. Additionally, lacosamide modulates collapsin response mediator protein 2, influencing phosphorylation-dependent processes that support axonal stability and neuroprotection [6-8].

Pharmacokinetically, lacosamide demonstrates linear and predictable behavior over the therapeutic range (100-800 mg/day), low plasma protein binding (< 15%), and an elimination half-life of approximately 13 hours [3,7]. It is rapidly absorbed and widely distributed; it effectively penetrates the central nervous system. Approximately 40% of the dose is excreted unchanged in the urine, and the remainder undergoes hepatic metabolism [4,8-11]. Despite these favorable properties, substantial interindividual variability in serum concentrations has been reported, complicating dose optimization and therapeutic drug monitoring, particularly in critically ill patients [6,12].

Acute kidney injury is common in the intensive care unit and frequently requires renal replacement therapy [13,14]. Continuous renal replacement therapy (CRRT) is often preferred because it provides greater hemodynamic stability and more gradual solute removal. However, CRRT profoundly alters drug disposition by increasing distribution volume, modifying extracorporeal clearance, and enabling drug adsorption to membrane surfaces [15,16]. These effects are particularly relevant for small, hydrophilic, weakly protein-bound agents such as lacosamide, which are efficiently removed by extracorporeal circuits [17].

Much of the available literature regarding CRRT-associated drug removal is based on case reports or small cohort studies; it typically reports overall extracorporeal drug loss or total clearance without isolating adsorption from diffusive and convective mechanisms. Consequently, estimates of CRRT clearance often conflate distinct processes and provide limited insight into membrane-material-dependent adsorption. Moreover, mechanistic in vitro studies that control experimental conditions to quantify adsorption independently, particularly across different membrane chemistries and matrices (saline vs plasma), remain scarce. This limited evidence base hampers dosing precision, especially during the early hours of filter use or after filter replacement, when adsorption-mediated losses may be most pronounced.

Membrane composition (eg, polyacrylonitrile [PAN], surface-modified PAN, and polysulfone [PS]) varies in terms of hydrophobicity, polymer chemistry, and surface charge, all of which comprise known determinants of nonspecific binding and protein corona formation. These surface properties can produce material-specific adsorption profiles, potentially resulting in differential reductions in circulating drug concentrations even when convective and diffusive parameters are held constant. Lacosamide is a small, hydrophilic, and minimally protein-bound drug. These properties may render it susceptible to membrane adsorption, which could meaningfully contribute to early drug losses and subtherapeutic exposure during CRRT.

Although lacosamide removal during CRRT is anticipated based on its physicochemical properties, the relative contribution of adsorption—quantified independently of diffusion and convection—and its dependence on membrane material remain poorly defined. Efforts to address this gap require a study design that isolates adsorption from other clearance mechanisms, systematically compares clinically relevant membrane chemistries, and evaluates matrix effects relevant to clinical practice.

To address these limitations, we utilized a closed-loop in vitro system specifically designed to isolate and quantify adsorption under controlled hydrodynamic conditions, thus minimizing or eliminating diffusive and convective solute removal. We systematically compared 3 clinically relevant dialysis membrane materials—PAN, polyethyleneimine-coated polyacrylonitrile (PAN-PEI), and PS—in 2 matrices (saline and plasma) to evaluate the extent and kinetics of lacosamide adsorption. By explicitly distinguishing adsorption from diffusive and convective clearance, this study addresses the unresolved question of membrane-material-dependent adsorption and clarifies its implications for dosing precision during extracorporeal therapy.

Material and Methods

Biological Material

Bovine blood was used in this study for both ethical and practical reasons. The use of human blood was considered inappropriate due to the large sample volumes required for the

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experimental design. Pooling blood from multiple human donors would introduce pronounced biological variability and reduce reproducibility, whereas collection from a single donor would present ethical and logistical challenges. Furthermore, human blood is a limited clinical resource reserved for therapeutic purposes, making its use for in vitro research ethically unjustifiable at this stage.

Although qualitative differences exist between human and bovine blood, previous research has demonstrated substantial similarities in plasma protein composition and binding characteristics [7]. Lacosamide exhibits low plasma protein binding (< 15%), suggesting that the presence of plasma proteins has minimal influence on its pharmacokinetics or interaction with dialysis membranes.

Immediately after collection, bovine blood was anticoagulated using a 7.4% sodium citrate solution (30 mL per liter of blood). Sodium citrate acts by chelating calcium ions, thus preventing activation of the coagulation cascade without altering plasma protein conformation. Citrate exhibits negligible protein binding (< 10%); no direct chemical interactions between sodium citrate and lacosamide have been reported in the literature.

Under Polish law (Act of 15 January 2015 on the Protection of Animals Used for Scientific or Educational Purposes), approval from an ethics committee is not required for studies using postmortem samples obtained from animals that were not subjected to any experimental procedures while alive.

Experimental Setup

The primary objective of this study was to assess lacosamide adsorption onto dialysis membranes commonly used in CRRT. Three membrane types were evaluated: PS (AV1000S, Fresenius Medical Care, Germany) with a surface area of 1.8 m^2, PAN-PEI (AN69ST150, Baxter International Inc., USA) with a surface area of 1.5 m^2, and PAN (AN69HF M150, Baxter International Inc.) with a surface area of 1.5 m^2.

To distinguish direct drug-membrane interactions from matrix-related effects, experiments were performed using both 0.9% NaCl and plasma. The saline model allowed assessment of intrinsic adsorption to the membrane material, whereas the plasma model was intended to reflect conditions in which membrane surfaces may be conditioned by plasma proteins, potentially modifying drug-membrane interactions.

Experiments were conducted using a closed-loop in vitro hemofiltration circuit equipped with a multiFiltrate dialysis machine (Fresenius Medical Care) and a multiFiltrate Kit 7 HV-CVVH 1000 (Fresenius Medical Care). The total circuit volume was 200 mL. All tests were conducted in continuous veno-venous hemofiltration (CVVH) mode. No additional calibration procedures beyond standard device setup were performed specifically for this study. Before each run, the system was primed with 0.9% sodium chloride solution to remove air and equilibrate the tubing and filter surfaces. The priming solution was then drained, and a reservoir containing 1000 mL of either bovine plasma or 0.9% NaCl was connected. Lacosamide was added as a commercial intravenous formulation (Vimpat®, UCB Pharma; 200 mg/20 mL), yielding a final volume of 1020 mL after mixing.

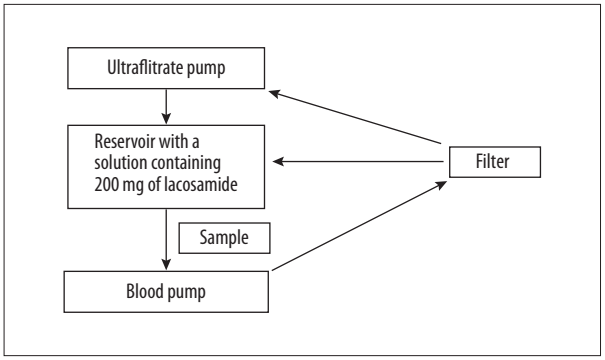

Figure 1. Schematic representation of the in vitro system used for continuous veno-venous hemofiltration.

CVVH Parameters

CVVH experiments were conducted under standardized conditions with a blood flow rate of 100 mL/min and an ultrafiltration rate of 600 mL/h. Temperature was maintained between 35 °C and 37 °C using a GUARDIAN 5000 heater (OHAUS, USA). Continuous pH monitoring during circulation was not performed. The filtrate was continuously recirculated into the reservoir to maintain a closed-loop recirculating system, thus eliminating convective drug loss (**Figure 1**).

For each filter type and test medium (plasma or saline), 3 independent experiments were conducted (n = 3 per group). Samples (3 mL) were withdrawn from the pre-pump sampling port at baseline (0 minutes) and after 5, 15, 30, 45, 60, and 90 minutes of perfusion. Blood samples were centrifuged at 3000 rpm for 10 minutes to obtain plasma. Plasma and saline samples were immediately frozen at -80 °C and transported to an analytical laboratory for quantification of lacosamide concentrations.

Control Experiments: Drug Stability Assessment

To confirm the chemical stability of lacosamide under the experimental conditions, control experiments were conducted in parallel using 0.9% NaCl or bovine plasma containing lacosamide (20 mL Vimpat® added to 1000 mL medium; total volume, 1020 mL). These solutions were incubated at 35 °C to

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37 °C without hemofiltration. Samples (3 mL) were collected at the same time points (0-90 minutes) to evaluate potential spontaneous degradation of the drug.

Statistical Analysis

Concentrations are expressed as mean ± standard deviation. Data normality was assessed using the Shapiro-Wilk test. For each filter condition (PAN-PEI, PAN, and PS), 3 independent experimental runs were conducted (n = 3 per filter). Each run included repeated measurements of lacosamide concentration at consecutive time points (0, 5, 15, 30, 45, 60, and 90 minutes). Each experimental run was treated as an independent experimental unit, and multiple time point measurements within a single run were treated as repeated observations. A mixed-effects repeated-measures model, with time as the within-run factor and filter type as the between-run factor, was used to evaluate overall time-dependent changes, differences among filter types, and the time × filter interaction. Additionally, separate repeated-measures analysis of variance (RM-ANOVA) assessments were performed for each filter condition to examine within-filter changes over time. The assumption of sphericity was evaluated using Mauchly's test, and no violations were detected. When a significant effect was observed, post hoc pairwise comparisons between time points were performed using Tukey's honestly significant difference test. These analyses were conducted separately for each filter condition and were restricted to within-filter comparisons. To evaluate overall adsorption during the experiment, the difference in concentration between baseline (T0) and 90 minutes (T90) was calculated. These differences were compared within individual filters using paired t-tests and among filter types using 1-way analysis of variance (ANOVA) followed by Tukey's post hoc test. *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using Statistica version 13 (https://www.statsoft.pl; StatSoft, Poland).

Results

Control Experiments: Stability of Lacosamide

To exclude the possibility of spontaneous degradation of lacosamide in solution, control experiments were performed by measuring drug concentrations in 0.9% NaCl and plasma samples. In saline, the concentration was 160.59 µg/mL at 0 minutes and 166.04 µg/mL at 90 minutes (difference: 3.39%). In plasma, the lacosamide concentration was 134.73 µg/mL at 0 minutes and 125.49 µg/mL at 90 minutes (difference: 6.86%). Based on these results, no spontaneous degradation of lacosamide was observed in either 0.9% NaCl or plasma over the study period.

Lacosamide Adsorption in 0.9% NaCl Solution

A mixed-effects model revealed a significant effect of time on lacosamide concentration ($P < 0.001$) and a significant effect of filter type ($P < 0.001$). No significant interaction between time and filter type was observed ($P = 0.49$), indicating that although overall concentration levels differed among filters, time-dependent profiles were similar across all filter types. However, the small sample size (n = 3) limits confidence in excluding membrane-specific effects.

Within-filter analyses showed time-dependent changes in lacosamide concentration for each filter type. For the PAN-PEI filter, a significant reduction in lacosamide concentration was observed between 0 and 15 minutes (RM-ANOVA, $P = 0.047$; Tukey's post hoc test, $P = 0.038$); no further statistically significant changes were noted at later time points. The total reduction between 0 and 90 minutes was 14.73% (**Table 1**).

For the PAN filter, a significant decrease in lacosamide concentration was observed from 15 minutes onward (RM-ANOVA, $P = 0.004$; Tukey's post hoc test: $P = 0.016$ at 15 minutes, $P = 0.003$ at 30 minutes, $P = 0.008$ at 45 minutes, $P = 0.008$ at 60 minutes, and $P = 0.011$ at 90 minutes). The total reduction at 90 minutes was 20.71% (**Table 1**).

Analysis of the PS filter showed significant differences in concentration between 0 minutes and all subsequent time points from 15 to 90 minutes (RM-ANOVA, $P = 0.005$; Tukey's post hoc test: $P = 0.040$ at 15 minutes, $P = 0.005$ at 30 minutes, $P = 0.014$ at 45 minutes, $P = 0.012$ at 60 minutes, and $P = 0.010$ at 90 minutes). The reduction between 0 and 90 minutes was 33.52% (**Table 1**).

When mean concentration changes between 0 and 90 minutes were compared among filter types, no statistically significant differences were observed ($P = 0.11$; **Table 1, Figure 2**). Notably, the limited sample size (n = 3 per filter type) reduced statistical power to detect between-filter differences.

Lacosamide Adsorption in Plasma

A mixed-effects model revealed a significant effect of time on lacosamide concentration in plasma ($P < 0.001$), whereas no significant effect of filter type was observed ($P = 0.77$) for the number of trials conducted with each filter (n = 3). No significant interaction between time and filter type was found ($P = 0.79$), indicating that overall concentration levels and time-dependent profiles were comparable across all filters.

Statistically significant changes in plasma lacosamide concentrations were observed for all 3 filters between baseline and time points from 5 to 90 minutes. Additionally, for the

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Table 1. Changes in lacosamide concentration in 0.9% NaCl solution between baseline (T0) and 90 minutes (T90).

Filter type	Lacosamide concentration T0 Mean ± SD	Lacosamide concentration T90 Mean ± SD	Percentage difference between T0 and T90	Mean ± SD change between T0 and T90
PAN PEI	171.06 ± 16.0	145.86 ± 1.0	14.73%	-25.2 ± 16.0
PAN	181.12 ± 3.8	143.6 ± 7.6	20.71%	-37.5 ± 9.7
PS	179.2 ± 3.9	119.14 ± 25.0	33.52%	-60.1 ± 22.7

Notes: For comparisons of mean concentrations between T0 and T90 within the PAN-PEI, PAN, and PS filter groups using paired t-tests, the *P* values were 0.11, 0.02, and 0.04, respectively. For comparison of mean concentration changes among the 3 filter types using 1-way ANOVA, the *P* value was 0.11. Abbreviations: ANOVA, analysis of variance; PAN, polyacrylonitrile; PAN-PEI, polyacrylonitrile polyethyleneimine; PS, polysulfone; SD, standard deviation.

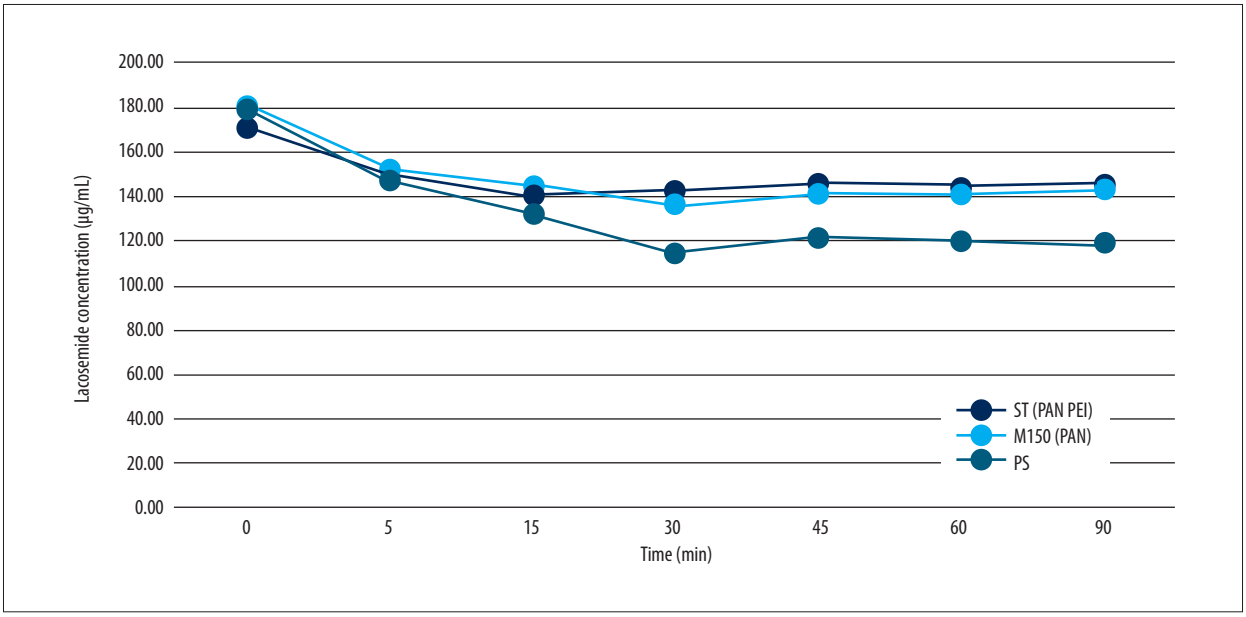

Figure 2. Changes in lacosamide concentration in 0.9% NaCl solution during the 90-minute experiment using 3 filter types: ST (PAN-PEI), M150 (PAN), and PS. Abbreviations: M150, AN69HF M150 filter; PAN, polyacrylonitrile; PAN-PEI, polyacrylonitrile polyethyleneimine; PS, polysulfone; ST, AN69ST150 filter.

PAN filter, a significant difference was observed between 5 and 90 minutes.

For the PAN-PEI filter, a significant decrease in concentration over time was observed (RM-ANOVA, $P < 0.001$). Tukey's post hoc test demonstrated significant differences at 5 minutes ($P < 0.002$) and at all subsequent time points (15, 30, 45, 60, and 90 minutes; all $P < 0.001$). The total reduction from baseline to 90 minutes was 23.04% (**Table 2, Figure 3**).

For the PAN filter, a significant reduction in lacosamide concentration was also observed over time (RM-ANOVA, $P < 0.001$). Post hoc comparisons confirmed significant differences between baseline and all subsequent time points (all $P < 0.0001$). The total reduction in lacosamide concentration was 27.71% (**Table 2, Figure 3**).

For the PS filter, significant differences were observed between baseline and time points from 15 to 90 minutes (RM-ANOVA, $P = 0.009$; Tukey's post hoc test: $P = 0.01$ at 15 minutes, $P = 0.01$ at 30 minutes, $P = 0.03$ at 45 minutes, $P = 0.01$ at 60 minutes, and $P = 0.02$ at 90 minutes). The total reduction at 90 minutes was 17.96% (**Table 2, Figure 3**).

Adsorption kinetics were consistent across all 3 independent experimental runs. Comparison of mean concentration changes between 0 and 90 minutes showed no statistically significant differences among filter types ($P = 0.09$; **Table 2**). Given that lacosamide exhibits low plasma protein binding (~15%), albumin concentrations were not measured—they were not expected to substantially influence adsorption.

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Table 2. Changes in lacosamide concentration in plasma between baseline (T0) and 90 minutes (T90).

Filter type	Lacosamide concentration T0 Mean ± SD	Lacosamide concentration T90 Mean ± SD	Percentage difference between T0 and T90	Mean ± SD change between T0 and T90
PAN PEI	182.08 ± 9.1	140.13 ± 12.4	23.04%	-42.0 ± 4.5
PAN	175.11 ± 2.6	126.59 ± 6.2	27.71%	-48.5 ± 4.9
PS	175.71 ± 25.3	144.15 ± 29.2	17.96%	-31.6 ± 11.7

Notes: For comparisons of mean concentrations between T0 and T90 within the PAN-PEI, PAN, and PS filter groups using paired t-tests, the *P* values were 0.004, 0.003, and 0.04, respectively. For comparison of mean concentration changes among the 3 filter types using 1-way ANOVA, the *P* value was 0.09. Abbreviations: ANOVA, analysis of variance; PAN, polyacrylonitrile; PAN-PEI, polyacrylonitrile polyethyleneimine; PS, polysulfone; SD, standard deviation.

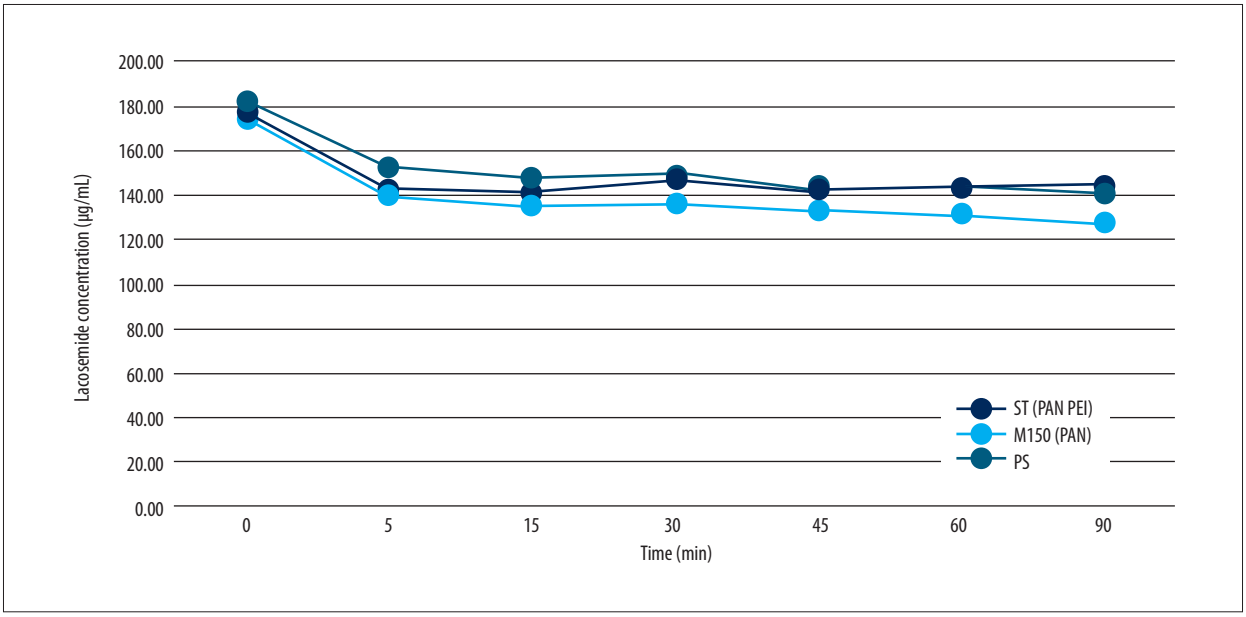

Figure 3. Changes in plasma lacosamide concentration during the 90-minute experiment using 3 filter types: ST (PAN-PEI), M150 (PAN), and PS. Abbreviations: M150, AN69HF M150 filter; PAN, polyacrylonitrile; PAN-PEI, polyacrylonitrile polyethyleneimine; PS, polysulfone; ST, AN69ST150 filter.

Discussion

The elimination of lacosamide during CRRT has been only rarely studied; the mechanistic basis of extracorporeal drug loss, particularly the contribution of membrane adsorption, remains poorly characterized. Thus, the present study was designed to examine lacosamide adsorption across 3 commonly used dialysis membrane materials in both saline and plasma and to assess its stability under these conditions, with the aim of providing mechanistic data relevant to CRRT management.

The present study confirmed that lacosamide remains chemically stable in both 0.9% NaCl and plasma for at least 90 minutes, excluding spontaneous degradation as a cause of concentration decline. This observation is consistent with previous pharmacokinetic data indicating that lacosamide is chemically stable in biological fluids and is not subject to hydrolytic or enzymatic degradation under standard conditions [7,18]. Accordingly, any reduction in measured drug concentration under dialysis conditions can be primarily attributed to dialysis-membrane adsorption or diffusion-mediated removal.

Our results demonstrate that lacosamide undergoes measurable adsorption to dialysis membranes in both saline and plasma. In saline, reductions of 14.7% to 33.5% were observed at 90 minutes; most adsorption occurred rapidly within the first 15 minutes.

Lacosamide is a hydrophilic compound containing an amide group, an aromatic ring, and oxygen and nitrogen atoms

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capable of forming hydrogen bonds. In contrast, dialysis membranes such as PAN, PAN-PEI, and PS contain polar functional groups and surface charges that can interact with polar drug molecules. Potential mechanisms include hydrogen bonding between the amide group of lacosamide and oxygen- or nitrogen-containing groups on the polymer surface, as well as electrostatic interactions between molecular dipoles and charged membrane groups. These interactions are physicochemical and nonspecific in nature; their magnitude likely depends on factors such as pH, solution composition, and membrane surface charge. Further studies are needed to characterize these mechanisms in greater detail.

Adsorption was more pronounced in plasma than in saline for the PAN-PEI and PAN membranes, with reductions of 18% to 28% at 90 minutes. Given the low plasma protein binding of lacosamide (approximately 15%), the observed losses are unlikely to primarily result from protein-drug interactions. Instead, they appear to reflect direct drug-membrane binding, consistent with reported mechanisms for other low-protein-bound agents used in critical care [19].

The slightly greater adsorption observed in plasma might also reflect secondary matrix effects, such as membrane conditioning by plasma proteins that alter surface hydrophobicity and charge, thus promoting nonspecific adsorption. These findings support a mechanistic interpretation in which adsorption may substantially contribute to lacosamide loss in extracorporeal systems.

A limitation of the present study is its use of bovine plasma rather than human plasma, which may influence membrane conditioning and, consequently, drug-membrane interactions. Although bovine and human plasma exhibit similarities in overall protein composition [20], qualitative and quantitative differences in specific plasma proteins and their adsorption behavior on dialysis membranes cannot be excluded. Such differences could affect the formation of a protein layer on the membrane surface and thereby modulate nonspecific drug adsorption. However, given the low plasma protein binding of lacosamide [21] and the physicochemical nature of its interaction with membrane materials, these effects are unlikely to be primary determinants of the observed adsorption phenomena. Importantly, the demonstration of measurable lacosamide adsorption in bovine plasma suggests that similar interactions can also occur in human plasma, although the magnitude of this effect under clinical conditions cannot be fully predicted. Therefore, whereas the present findings support the relevance of adsorption as a contributing mechanism of extracorporeal lacosamide loss, extrapolation to human plasma should be made with caution. Further investigation is warranted in clinically representative models.

The scarcity of published data regarding lacosamide elimination during CRRT enhances the need for contextualization of the present findings. Clinical studies indicate that hemodialysis can remove up to 50% of circulating lacosamide during a standard 4-hour session [22,23]. Based on the pharmacokinetic data reported by Gábor et al [23], lacosamide, given its low plasma protein binding and small molecular weight, can be partially cleared during CRRT; elimination primarily depends on the intensity of the filtration process.

Among the few available studies, Wieruszewski et al described the pharmacokinetics of lacosamide in a critically ill adult and reported pronounced extracorporeal elimination during CVVH, leading to subtherapeutic drug concentrations, a finding consistent with the present results [24]. Similarly, Franquiz et al reported a case of status epilepticus requiring CVVH in which lacosamide administered at 2 × 200 mg was removed by the extracorporeal circuit, although plasma concentrations remained within the target range throughout the dosing period [25]. High lacosamide clearance during renal replacement therapy was also documented by Kalaria et al [26] in 7 patients admitted to a neurological intensive care unit. The authors concluded that lacosamide clearance increases with higher effluent flow rates and that dosing regimens should be adjusted to achieve exposures comparable to those observed in patients with normal renal function. Taken together, these limited reports consistently suggest that CRRT poses a clinically meaningful risk of lacosamide underexposure, underscoring the need for mechanistic data such as those provided by the present study.

The present in vitro findings are consistent with these clinical observations, demonstrating that measurable drug loss can occur over a substantially shorter period and in the absence of dialysis fluid flow. Such observations suggest that adsorption alone—independent of dialysate-mediated diffusion—could strongly contribute to lacosamide removal from circulation. Rapid early adsorption may be clinically important during the initiation of dialysis or CRRT, when abrupt reductions in drug concentration could increase seizure risk in vulnerable patients. Further studies are needed to confirm the extent of lacosamide adsorption to dialysis membranes and to determine the clinical implications of this phenomenon.

In our in vitro study, we used 200 mg of lacosamide in 1000 mL of plasma or 0.9% NaCl solution. This corresponds to the standard single dose administered to patients with status epilepticus. Unfortunately, published lacosamide dosing regimens have primarily been developed from adult case reports [24,25]. Kalaria et al [26] proposed dosage adjustments ranging from 100 to 600 mg/day, depending on effluent flow rates of 1 to 3.5 L/h. For CRRT with higher flow rates (> 3.5 to 5 L/h), a lacosamide dose of 600 to 800 mg/day was recommended. Expert

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recommendations have also suggested therapeutic drug monitoring to guide dose adjustments by maintaining trough concentrations within the range of 5 to 10 mg/L or an area under the concentration-time curve of at least 94 mg·h/L [26]. Currently, no lacosamide dosing regimens incorporating both pharmacokinetic and pharmacodynamic assessments have been established for critically ill patients undergoing CRRT.

Numerical differences in adsorption were observed among the 3 membrane materials tested—PAN-PEI, PAN, and PS. However, these differences were not statistically significant. This finding contrasts with observations regarding lipophilic anesthetics such as propofol and midazolam, for which membrane composition greatly influences adsorption [27]. The lack of significant polymer-specific differences suggests that lacosamide adsorption represents a generalizable characteristic across dialysis membranes, rather than a strictly material-dependent phenomenon. Nevertheless, subtle physicochemical differences among membranes, including surface charge density and hydrophilic coating composition, may influence adsorption kinetics under dynamic flow conditions.

The magnitude of drug loss observed in plasma, approaching 30% after 90 minutes, may be clinically relevant. A limitation of our study is the small number of experiments performed with each filter type. Further research is needed to confirm the adsorption phenomenon and clarify its clinical implications. However, lacosamide exhibits dose-dependent antiepileptic efficacy and has a relatively narrow therapeutic range [3]. Consequently, even moderate reductions in circulating concentrations during dialysis or CRRT can result in subtherapeutic exposure, particularly in critically ill patients for whom consistent seizure control is essential. Current clinical guidelines already recommend supplemental lacosamide dosing after hemodialysis [10]. The present findings provide mechanistic evidence in support of these recommendations by demonstrating that adsorption alone can substantially contribute to total drug loss during extracorporeal therapy.

In patients with renal failure and critical illness, the free fraction of lacosamide may increase. Several physiological processes may contribute to this effect. Uremic toxins can cause carbamylation and oxidation of albumin, reducing its affinity for the drug and thus increasing the free fraction of lacosamide. Some uremic toxins are hydrophobic and may occupy adsorption sites on dialysis membranes. Changes in lipid composition, including membrane lipid peroxidation and alterations in the cholesterol-to-phospholipid ratio, may influence the membrane-plasma partitioning of lacosamide, although no standardized partition coefficient between dialysis membranes and plasma has been reported for this drug. In renal failure, a protein-lipid layer can form on the filter surface, potentially increasing nonspecific drug adsorption. Metabolic acidosis and hyperosmolality may also affect adsorption kinetics, although available evidence suggests that pH has a greater effect on dialysis clearance than on adsorption. Increased concentrations of lipoproteins, C-reactive protein, and fibrinogen, as well as elevated plasma viscosity, may cause slower diffusive transport of the drug to the membrane surface [24,25,28].

The results of our study indicate that lacosamide may undergo adsorption to dialysis membranes during extracorporeal therapy. However, these findings require confirmation through additional in vitro and clinical studies. Factors such as altered protein binding in uremic plasma, changes in drug distribution during critical illness, and the concurrent administration of other medications can further increase pharmacokinetic variability. These variables should be carefully considered when managing lacosamide therapy in patients who require renal replacement therapy. Routine therapeutic drug monitoring and individualized dose adjustments may be necessary to maintain optimal plasma concentrations.

Given the paucity of data regarding lacosamide elimination during CRRT, the present study provides new mechanistic insights into the interaction between lacosamide and dialysis membranes, demonstrating that adsorption can substantially reduce drug concentrations in saline and plasma. These findings highlight the importance of adjusting for extracorporeal drug losses when managing antiepileptic therapy in patients undergoing dialysis or CRRT. Future research should evaluate adsorption under dynamic flow conditions, using clinically relevant blood-membrane contact times and concomitant drug administration, to better replicate in vivo conditions and refine dosing strategies for clinical practice.

Limitations of the Study

The sample size for each filter was limited to 3 independent experiments (n = 3 per filter). This small sample size reduced statistical power; therefore, nonsignificant differences among filters should be interpreted with caution.

Conclusions

In this in vitro hemofiltration model, lacosamide remained chemically stable in both saline and plasma but exhibited consistent, measurable adsorption to PAN, PAN-PEI, and PS membranes, resulting in approximately 15% to 30% reductions in concentration over 90 minutes. Greater adsorption was observed in plasma with the PAN and PAN-PEI filters. Adsorption predominantly occurred during the early phase of circulation and did not significantly differ among membrane types, suggesting a material-independent interaction under the tested conditions. However, the small sample size limits confidence in excluding membrane-specific effects.

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These findings indicate that membrane adsorption may contribute to decreased circulating lacosamide concentrations during CRRT or hemodialysis, beyond losses linked to diffusive clearance alone. However, the closed-loop in vitro design, use of bovine plasma, limited observation period, and absence of dynamic clinical variables restrict direct extrapolation to patient care. Given these limitations, the findings support consideration of extracorporeal drug loss and the potential need for concentration-guided dose adjustments in critically ill patients receiving renal replacement therapy.

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Department and Institution Where Work Was Done

Department of Pharmacology and Toxicology, Faculty of Medicine, University of Warmia and Mazury, Olsztyn, Poland

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