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Evaluation of the Pharmacokinetics of Nafamostat Mesylate during Continuous Renal Replacement Therapy

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Abstract

Continuous renal replacement therapy (CRRT) is the preferred dialysis modality in critical care settings for patients with hemodynamic instability. Nafamostat mesylate (NM) is an anticoagulant commonly used (mainly in Japan) during CRRT in patients with high bleeding risk. In this study, we evaluated the pharmacokinetics of NM during CRRT. Patients undergoing CRRT therapy and using NM as the anticoagulant in the intensive care unit were enrolled in the study. Blood was collected from the CRRT circuit just after blood removal, just before and after the membrane for CRRT, and from the filtrates after the membrane. NM concentrations were measured using high-performance liquid chromatography. NM was detected in the intracorporeal circulation during CRRT in some cases, and liver enzymes were severely elevated in almost all of the cases. Coagulation time was prolonged even before the initiation of NM administration in these cases and may be associated with liver damage. This study suggests that NM dosage should take into account liver damage assessed by elevated liver enzymes.

Keywords

Nafamostat Mesylate, Continuous Renal Replacement Therapy, Liver Dysfunction

1. Introduction

Continuous renal replacement therapy (CRRT) is the preferred dialysis modality for patients who are hemodynamically unstable in critical care settings. Nafamostat mesylate (NM) is commonly used (mainly in Japan) as an anticoagulant

for CRRT [1]-[6]. NM is a synthetic serine protease inhibitor originally developed as a therapy for pancreatitis. However, due to its inhibition of platelet aggregation and coagulation factors [7], NM is increasingly used as an anticoagulant during CRRT. NM has a very short half-life and can act as a regional anticoagulant in the extracorporeal circulation [8]. Therefore, NM is commonly used as an anticoagulant, especially in patients at high risk for bleeding during CRRT [2] [7]. In addition, NM anticoagulation was associated with prolonged filter survival and decreased incidence of bleeding complications compared with heparin [9] [10]. Besides, it has been suggested that anticoagulation with NM during extracorporeal membrane oxygenation might be a feasible and safe alternative of heparin for critically ill patients with high-risk bleeding [11]. However, the pharmacokinetics of NM in the intracorporal and extracorporeal circulations during CRRT is not clear. In addition, the effects of liver failure on the pharmacokinetics of NM have not been investigated. In this study, we investigated the pharmacokinetics of NM in the intracorporal and extracorporeal circulations during CRRT in the critical care setting.

2. Material and Methods

This prospective observational trial in a single-center was approved by the Ethics Committee of Nara Medical University Hospital (approval number: 794), and the trial was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN ID: 000048844). The trial was conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement [12].

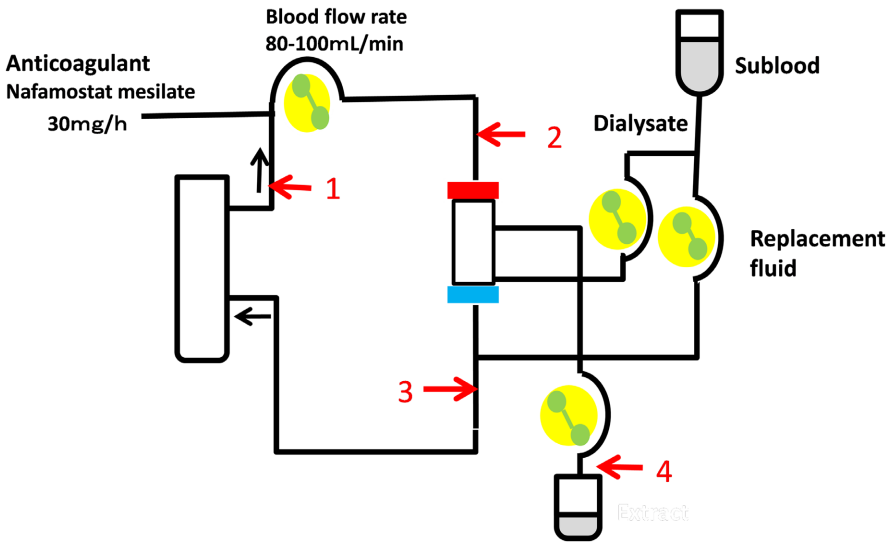
2.1. Patients

Inclusion criteria were patients who received CRRT and NM was used as an anticoagulant in the intensive care unit (ICU) during CRRT. Written informed consent was obtained before blood sample collection. Written informed consent was obtained by the next of kin if a patient could not provide the consent. Patients were excluded from the study if they were pregnant (or might be pregnant), younger than 18 years, transfused with a blood preparation (concentrated red cells, fresh frozen plasma, and platelet) during the study period, or unable to continue CRRT for 24 hours due to circuit coagulation.

2.2. Experimental Protocols

Continuous hemodiafiltration (CHDF) was used for CRRT therapy in the ICU. The CHDF conditions were as follows: 1) blood flow rate of 80 - 100 ml/min, dialysate flow rate of 400 ml/hr, replacement fluid flow rate of 200 ml/hr, and ultrafiltration rate of 600 ml/hr or 2) blood flow rate of 80 - 100 ml/min, dialysate flow rate of 100 ml/hr, replacement fluid flow rate of 600 ml/hr and ultrafiltration rate of 700 ml/hr. A fixed dose of 30 mg/hr of NM was administered during CRRT. A commercially available polysulfone membrane (Excel flow 1.0^{R}, Asahi

Kasei Medical Co.Ltd.Tokyo, Japan) was used for CRRT. CRRT was performed using a blood purifying device (JUN-55X^{R}, Japan Lifeline Co. Ltd., Tokyo, Japan). Blood was sampled every six hours beginning with the initiation of CRRT and completed in 24 hours. Blood test results (platelet count, liver enzyme values, blood coagulation test, activated clotting time: ACT) were collected before the initiation of CRRT and 24 hours after CRRT was started (at that time, CRRT was temporarily terminated for circuit exchange). Figure 1 shows blood sampling points and filtrate sampling points from the CRRT circuit including the following: 1) just after blood removal through the vascular access (intracorporeal NM concentrations), 2) before the CRRT membrane (extracorporeal NM concentrations), 3) after the CRRT membrane (extracorporeal NM concentrations after filtration), and 4) the filtration drainage (NM concentrations in the filtrate). We measured NM concentrations in the cryopreserved plasma using high-performance liquid chromatography (HPLC), using measurement devices (pump: LC-20AT; ultraviolet/visible detector: SPD-20A; column oven: CTO-20AC; degasser: DGU-20A5R, from Shimadzu Co., Ltd., Kyoto, Japan). To remove proteins prior to injection, the plasma samples were prepared with a solid-phase extraction column (Oasis HLB3cc Extraction Cartridges, Japan Waters Co., Ltd., Tokyo, Japan). The mobile phase consisted of a solution A (6.07 g of sodium 1-heptanesulfonate dissolved in acetic acid diluted with 6 mL of acetic acid to 1000 mL with pure water to make a total volume of 1000 mL) and a solution B (acetonitrile) at a ratio of 100:0 (v/v%) to 0:100 (v/v%) after 8 minutes for linear gradient analysis.



CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Figure 1. Sampling points for collecting blood and filtrate during continuous renal replacement therapy. (CRRT) circuit, 1) the sampling point just after blood removal through the vascular access (intracorporeal nafamostat mesylate (NM) concentrations), 2) the sampling point before the CRRT membrane (extracorporeal NM concentrations), 3) the sampling point after the CRRT membrane (extracorporeal NM concentrations after filtration), 4) the sampling point of the filtration drainage (NM concentrations in the filtrate).

The measurement was performed with wavelength of 260 nm and column temperature at 40˚C.

2.3. Statistical Analysis

All data are shown as individuals and not summarized because the pharmacokinetics of NM in critical patients exhibit large differences among individuals. Data were categorized into two groups showing NM in the intracorporeal circulation and not showing NM in the intracorporeal circulation. A sample size calculation was not done because this was an observational exploratory research study.

3. Results

We excluded 4 of 24 cases. Two cases were excluded because NM was improperly detected in HPLC, one case was excluded because NM could not be distinguished from other drugs, and 1 case was excluded because CRRT was terminated before 24 hours. Table 1 shows patient characteristics.

Table 1. Characteristics of each patient.

Case No	Age	Gender	Height (cm)	Body weight (kg)	Disease	SOFA score
1	69	Female	145	54	sepsis	8
2	72	Female	156	44	sepsis, CKD	10
3	79	Male	178	65	sepsis	10
5	68	Male	167	68	sepsis	12
6	74	Male	165	75	angina pectoris, CKD	6
7	84	Male	160	49	sepsis	17
8	79	Male	157	59	sepsis	11
10	68	Male	163	61	carotid stenosis, CKD	5
11	66	Male	160	80	heart failure, MODS	9
12	71	Male	167	66	gallbladder cancer, sepsis	15
14	70	Male	170	67	AKI, sepsis	13
16	81	Male	162	50	sepsis	8
17	58	Male	168	68	acute abdomen	6
18	74	Male	167	53	pancreatic head cancer	6
19	87	Male	157	52	CKD	17
20	80	Female	154	53	pancreatic cancer, AKI	10
21	64	Female	150	60	acute pancreatitis	7
22	55	Female	160	46	AKI	4
23	85	Male	165	60	subarachnoid hemorrhage	7
24	80	Male	156	57	nephrotic syndrome	9

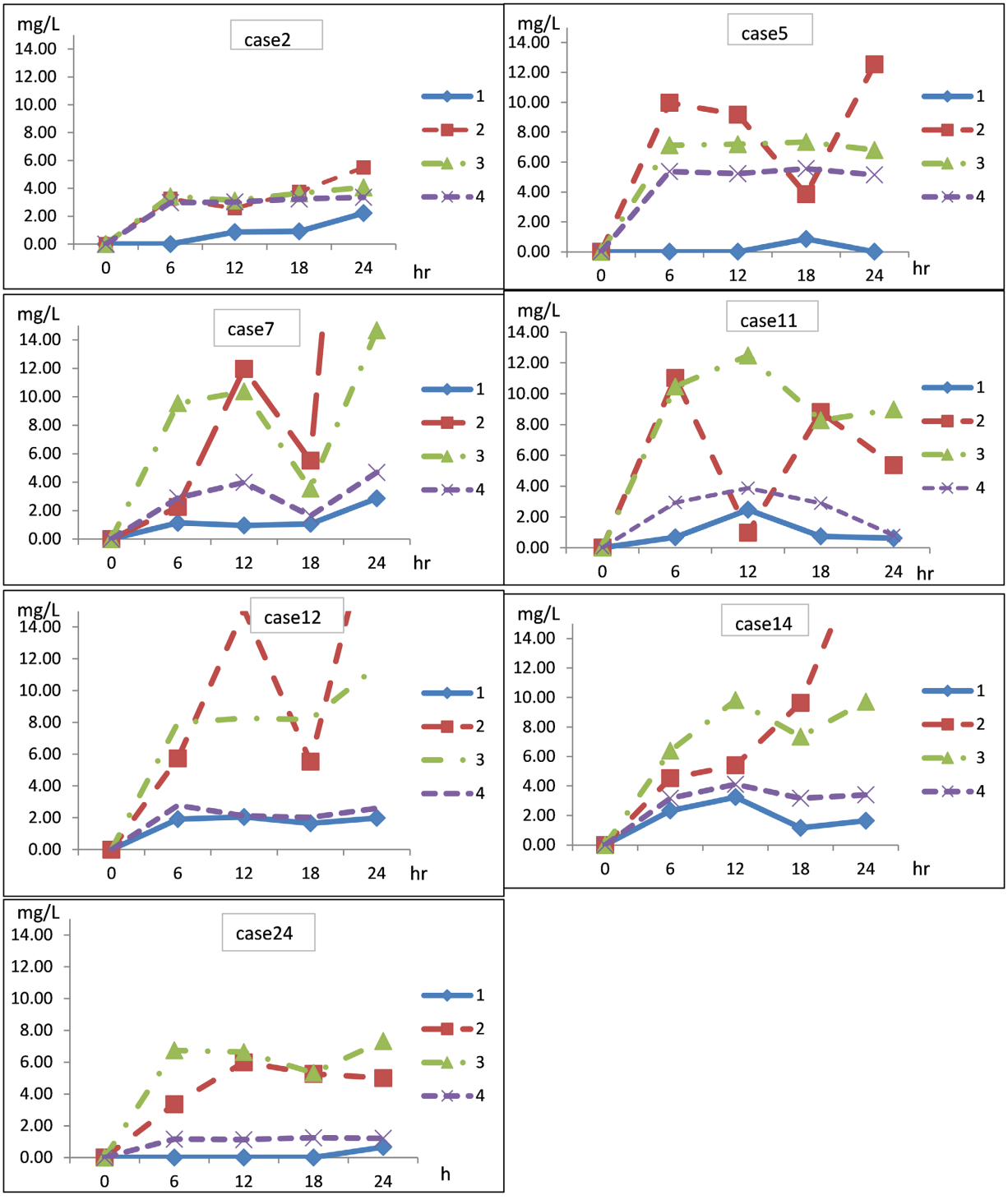
AKI, Acute kidney injury; CKD, Chronic kidney disease; MODS, multi-organ disease syndrome; SOFA, Sequential Organ Failure Assessment.

In cases 2, 7, 11, 12, 14, and 24, NM was detected in the intracorporeal circulation (sampling point 1) (**Figure 2**). NM concentrations in the extracorporeal circuit were high and fluctuated. Liver enzymes were elevated in almost all of these cases (**Table 2**). In cases 1, 3, 5, 6, 8, 10, and 16 - 23, NM was not detected in the intracorporeal circulation (sampling point 1) (**Figure 3**). In more than half of these cases, NM concentrations in the extracorporeal circuit were stable and low. However, concentrations of NM before and after the membrane for CRRT were unstable in some cases. Liver enzymes were close to normal ranges in all but one of these cases (**Table 3**). Regardless of NM concentrations in the intracorporeal circulation, concentrations of NM in the filtrates changed in proportion to concentrations of NM in the extracorporeal blood. Moreover, in most cases in which NM was detected in the intracorporeal circulation, coagulation time, especially activated partial thromboplastin time (APTT) and ACT, was prolonged before initiation of NM administration. These values were further prolonged after terminating NM administration. Fibrin degradation product and platelet count did not change much before and after NM administration (**Table 2**). This trend was common when NM was not detected in the intracorporeal circulation, but the values were not extreme.

4. Discussion

CRRT is widely used for treating critically ill patients, and NM is increasingly used as an anticoagulant during CRRT. NM is a safe and effective anticoagulant in CRRT patients with bleeding tendencies [2] [7]. NM inhibits platelet aggregation and coagulation factors, such as thrombin, Xa, XIIa, kallikrein, and complement system components. Thus, MN is more commonly used as an anticoagulant in CRRT since 1990 (mainly in Japan) [13] [14] [15] [16] [17]. NM is immediately hydrolyzed to amidinonaphthol (AN) and p-guanidinobenzoic acid by carboxylesterase, which is present in the blood and liver [1]. AN is metabolized to amidinonaphthol glucuronide (AN-glu) in the liver. NM is metabolized in a very short time. Because the anticoagulant action of NM is limited in the extracorporeal circulation due to its rapid elimination, NM should not have anticoagulant action in the intracorporeal circulation.

In this study, we evaluated the pharmacokinetics of NM during CRRT in the critical care setting. NM should be limited to the extracorporeal circulation, but we confirmed the presence of NM in the intracorporeal blood in some cases. Liver function and damage are evaluated using aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In particular, serum ALT activity is commonly measured to assess hepatic disease [18]. Most of the cases with NM in the intracorporeal blood also exhibited elevated liver enzymes. Thus, the presence of NM in the intracorporeal blood may be associated with liver damage. During liver damage, which was implied by elevated liver enzymes in this study, global production of metabolizing enzymes in the liver decreases, especially in critically ill patients. The decline in metabolizing enzymes probably contributed to the



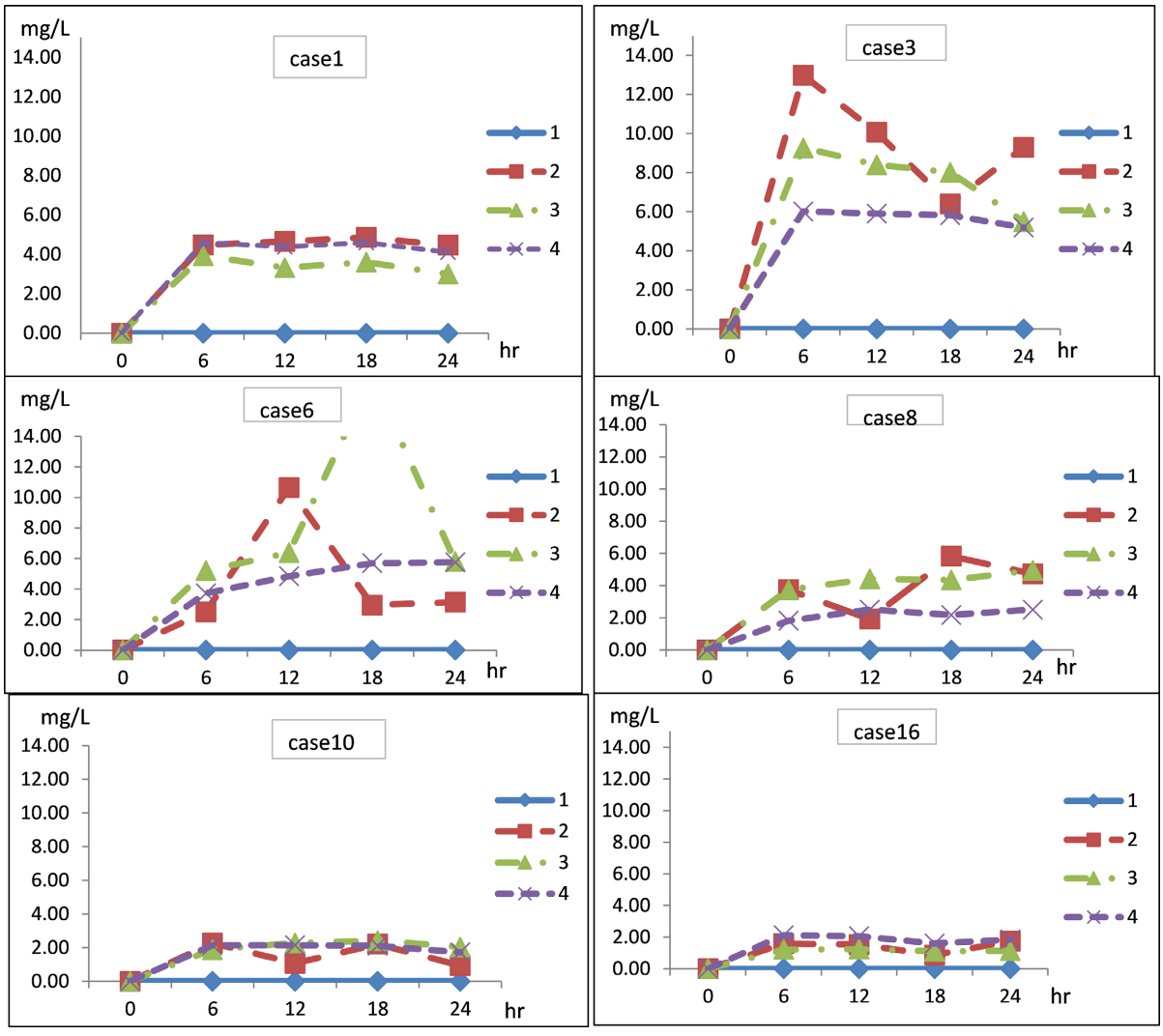
CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

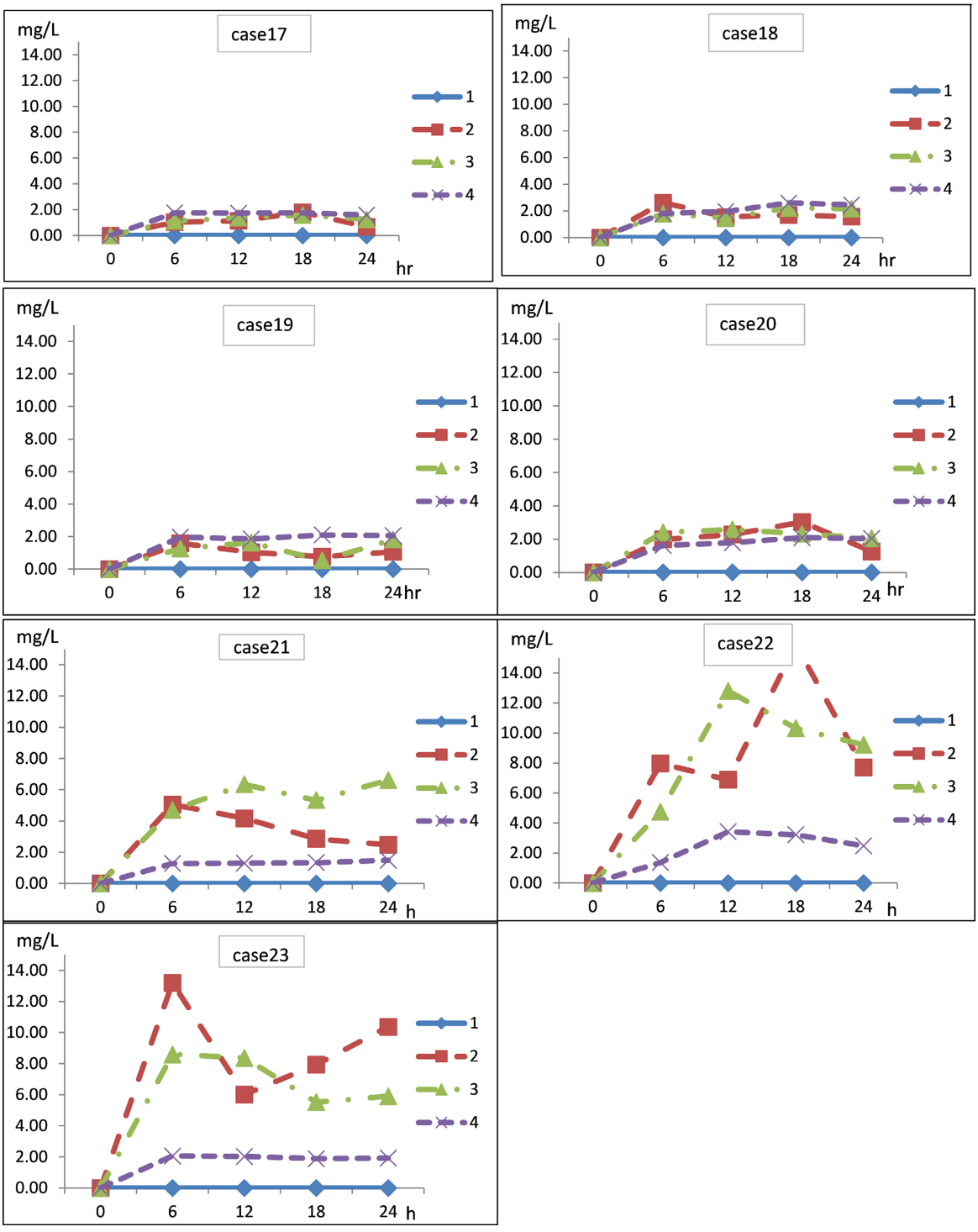
Figure 2. Changes in nafamostat mesylate (NM) concentrations from blood and filtrate during continuous renal replacement therapy (CRRT) circuit in patients with NM in the intracorporeal circulation. NM was detected in cases 2, 7, 11, 12, 14, and 24. Samples were obtained by drawing blood and filtrate from the CRRT circuit every 6 hours from the initiation to termination of CRRT. 1) the sampling point just after blood removal through the vascular access (intracorporeal nafamostat mesylate (NM) concentrations), 2) the sampling point before the CRRT membrane (extracorporeal NM concentrations), 3) the sampling point after the CRRT membrane (extracorporeal NM concentrations after filtration), 4) the sampling point of the filtration drainage (NM concentrations in the filtrate).

Table 2. Laboratory data of the patients with nafamostat mesylate in the intracorporeal circulation during continuous renal replacement therapy.

Patient	PT (sec) Pre/Post	APTT (sec) Pre/Post	FDP (μg/mL) Pre/Post	ACT (sec) Pre/Post	PLT (×10⁴/μL) Pre/Post	ALT (IU/L) Pre/Post	AST (IU/L) Pre/Post
2	19.4/16.3	36.5/76.6	85.9/84	147/183	43.3/33.9	170/157	908/925
5	16.7/15.1	60.7/88.2	11.9/15	180/216	4.0/2.2	25/189	32/265
7	28.3/59.1	41.5/180	56.2/22.9	295/479	10.4/5.0	400/744	722/1854
11	35/23.7	84.3/79.2	689/479	146/126	4.7/5.7	2160/1342	2340/825
12	18.5/21.7	50.2/162.7	29.5/26.9	152/177	11.7/10.8	197/101	173/73
14	13.5/14	30.2/40.4	20.0/10.4	98/136	10/14.6	123/89	120/66
24	11.9/12.2	31.6/37.4	11.6/14.7	165/149	6.5/9.0	46/80	47/67

ACT, activated clotting time; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FDP, fibrinogen/fibrin degradation products; PLT, platelet; PT, prothrombin time. Pre, laboratory data before the start of CRRT; Post, laboratory data after the termination of CRRT.





CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Figure 3. Changes in nafamostat mesylate (NM) concentrations in blood and filtrate during continuous renal replacement therapy circuit in patients with no NM in the intracorporeal circulation. NM was not detected in cases 1, 3, 5, 6, 8, 10, and 16 - 23. Samples were obtained by drawing blood and filtrate from the CRRT circuit every 6 hours from the initiation to termination of CRRT. 1) the sampling point just after blood removal through the vascular access (intracorporeal nafamostat mesylate (NM) concentrations), 2) the sampling point before the CRRT membrane (extracorporeal NM concentrations), 3) the sampling point after the CRRT membrane (extracorporeal NM concentrations after filtration), 4) the sampling point of the filtration drainage (NM concentrations in the filtrate).

Table 3. Laboratory data of the patients in which nafamostat mesylate was not detected in the intracorporeal circulation during continuous renal replacement therapy.

Patient	PT (sec) Pre/Post	APTT (sec) Pre/Post	FDP (μg/mL) Pre/Post	ACT (sec) Pre/Post	PLT (×10⁴/μL) Pre/Post	ALT (IU/L) Pre/Post	AST (IU/L) Pre/Post
1	17.1/11.2	94.9/50.8	45.3/24.1	130/117	3.7/4.4	69/32	93/24
3	15.6/13.7	180/115.3	56.3/23.8	156/172	3.8/1.8	24/22	25/20
6	14.9/14.8	31.3/61	53.6/33.3	208/227	10.6/7.5	68/53	323/101
8	16.4/18	58.6/81.9	31.1/30	185/178	9.7/6.6	9/10	40/45
10	13.5/11.6	37.4/56.1	16.4/12.5	208/155	16.6/14.3	17/27	99//98
16	16.5/15.8	53.9/86.8	18.4/7.8	192/208	10.9/7.3	21/17	52/36
17	16.5/13.4	41.2/44.2	11.8/12.7	162/158	14.5/13.0	24/23	34/31
18	13.6/15.4	25.9/65.9	6.8/12.1	141/147	21.7/10.5	11/16	29/50
19	16.9/16.7	52.3/64	75.2/58.4	189/175	4.3/5.0	251/205	277/173
20	16.8/17.1	79/80	24.8/27.4	187/192	10.7/10.4	32/21	52/61
21	12.9/13.4	43.1/45.2	33/44	130/140	3.8/5.2	56/47	39/34
22	18.2/17.1	49.1/45.2	5.7/5.8	162/175	20/17.7	14/14	13/18
23	13.0/12.6	34.1/41.1	13.4/12.6	152/141	23.8/23.9	20/23	21/21

ACT, activated clotting time; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FDP, fibrinogen/fibrin degradation products; PLT, platelet; PT, prothrombin time. Pre, laboratory data before the start of CRRT; Post, laboratory data after the termination of CRRT.

incomplete elimination of NM from the intracorporeal circulation. We did not measure NM concentrations after discontinuation of CRRT. Therefore, it is not known how long it takes to eliminate the residual NM for such liver damaged patients. We used a fixed dose of NM in this study. Therefore, this study results suggest that we had better use lower doses of NM for patients with liver damage.

5. Limitations

In this study, we did not evaluate blood coagulation, which may be a surrogate of NM pharmacodynamics, or residual NM because the condition of the current participants was too severe and complicated to evaluate the pharmacodynamics. However, in some cases, especially in patients with liver damage, coagulation time was considerably prolonged without NM (Table 1). Moreover, further prolonged coagulation times were observed in patients after termination of NM administration, probably due to residual MN in the blood (Table 1).

6. Conclusion

This study confirmed that NM used for CRRT therapy was usually not detected in the intracorporeal circulation. However, NM was detected in the intracorpo-

real circulation when liver damage was present. This study suggests that liver damage, evaluated by AST and ALT levels, should be considered when deciding on the NM dosage in patients undergoing CRRT.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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