—Original—

Physical Compatibility of Nafamostat with Analgesics, Sedatives, and Muscle Relaxants for Treatment of Coronavirus Disease 2019

Masayoshi Kondo, Makihiko Nagano, Mariko Yoshida, Naoki Yoshida, Naoya Tagui, Masato Yoshida, Kazutoshi Sugaya and Hisamitsu Takase

Department of Pharmacy, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

Background: Severe coronavirus disease 2019 (COVID-19) may require continuous administration of analgesics, sedatives, and muscle relaxants. Nafamostat has recently been reported as a therapeutic agent for COVID-19. However, there is a lack of information on the compatibility of nafamostat with the aforementioned drug classes. This study evaluated the physical compatibility of nafamostat with these drug classes.

Methods: Nafamostat was combined with 1-3 target drugs (fentanyl, morphine, midazolam, dexmedetomidine, and rocuronium). Fifteen physical compatibility tests were conducted. Nafamostat was dissolved in 5% glucose solution; the final concentration was 10 mg/mL. All other medications were diluted in 0.9% sodium chloride to obtain clinically relevant concentrations. The power of hydrogen (pH) of all medications was measured during each test. Compatibility tests were conducted with 4 test solutions in which nafamostat and the target drugs were compounded at equal volume ratios (1:1, 1:1:1, or 1:1:1:1). Visual appearance, turbidity, and pH were evaluated immediately after mixing and at 1 and 3 hours. Physical incompatibilities were defined as gross precipitation, cloudiness, appearance of the Tyndall effect, or a turbidity change of ≥0.5 nephelometric turbidity units (NTU) based on nafamostat.

Results: The mean pH of nafamostat was 3.13 ± 0.03. The combination of nafamostat, fentanyl, and dexmedetomidine had the highest pH (3.39 ± 0.01; 3 hours after mixing). All drugs were compatible with nafamostat until 3 hours after admixture, with a mean turbidity value of ≤0.03 NTU.

Conclusions: Infusions combining nafamostat with the tested sedatives, analgesics, and muscle relaxants could be safely administered. (J Nippon Med Sch 2021; 88: 533–539)

Key words: coronavirus disease (COVID-19), nafamostat, compatibility, drug administration route, power of hydrogen (pH)

Introduction

The first case of coronavirus disease 2019 (COVID-19) was reported in the People's Republic of China in December 2019, and COVID-19 subsequently spread to many countries, including Japan. Nafamostat is a therapeutic agent for pancreatitis and disseminated intravascular coagulation[1,2]. Continuous administration of nafamostat 200 mg/day (0.06-0.20 mg/kg/hour) has been used for treating disseminated intravascular coagulation. Nafamostat has been reported to block the activity of severe acute respiratory syndrome coronavirus 2 by inhibiting transmembrane protease serine 2[3] and has recently been reported as a therapeutic agent for COVID-19[4,5].

Patients with severe COVID-19 require mechanical ventilation during extracorporeal membrane oxygenation (ECMO) support[6–8], and it is assumed they will need continuous injections of drugs such as analgesics, sedatives, and muscle relaxants. COVID-19 increases the risk of thrombosis, and the International Society on Thrombosis and Hemostasis (ISTH) recommends prophylaxis with heparin for patients requiring hospitalization[9]. Nafamostat treatment for severe COVID-19 is thus likely to be

Correspondence to Masayoshi Kondo, Department of Pharmacy, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: kondomasayoshi@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-104
Journal Website (https://www.nms.ac.jp/sh/jnms/)

administered in combination with these injections.

In the intensive care unit (ICU), multiple drugs are often administered intravenously through the same catheter line. Different techniques are used to avoid drug incompatibility, such as changing the administration time for each drug or flushing with normal saline before and after each injection. However, in the case of continuous infusions such as nafamostat, the only way to avoid drug incompatibility is to use a separate line for each drug. Therefore, information on compatibility tests is important to avoid drug incompatibilities such as intravenous line blockages and turbidity.

Patients with severe COVID-19 may require several continuous injections of heparin, analgesics, sedatives, or muscle relaxants, which may have to be combined and administered through the same infusion route. A mixture of nafamostat and heparin causes physical incompatibility because it produces a sparingly soluble sulfate[10]. Compatibility tests between nafamostat and analgesics, sedatives, and muscle relaxants have not been carried out with morphine, dexmedetomidine, or rocuronium[10–13]. Additionally, only a few multi-drug compatibility tests, wherein 3 or more drugs were mixed, have been reported. However, drug compatibility tests for COVID-19 are not sufficient. Therefore, this study aimed to evaluate the physical compatibility of nafamostat with analgesics, sedatives, and muscle relaxants during simulated Y-site administration (an equal volume ratio) by visual inspection, turbidity evaluation, and power of hydrogen (pH) measurement.

Materials and Methods

Since this study was a drug compatibility study and not a clinical study, the ethics committee of Nippon Medical School Tama Nagayama Hospital deemed ethical review unnecessary. Analgesics, sedatives, and muscle relaxants are the drug classes commonly combined with nafamostat during the administration of injections through the infusion line for severe COVID-19. The analgesics chosen for this study were fentanyl and morphine, the sedatives were midazolam and dexmedetomidine, and the muscle relaxant was rocuronium. Although propofol is a frequently used sedative[14], it was excluded from this study because it is a fat emulsion, which would make its evaluation by visual inspection difficult.

Nafamostat (Lot NTC119W; Asahi Kasei Pharma Corporation) was dissolved in a 5% glucose solution (Lot 9J 96P; Otsuka Pharmaceutical Factory, Inc.) to obtain a solution with a concentration of 10 mg/mL. Morphine (Lot W5303; Shionogi Pharma Co., Ltd) and dexmedetomidine (Lot FPF002; Sandoz) were diluted in 0.9% sodium chloride (Lot 0A78P; Otsuka Pharmaceutical Factory, Inc.) to prepare solutions with concentrations of 2 mg/mL and 4 μg/mL, respectively. Fentanyl (Lot A0015; Terumo), midazolam (Lot JF5569; Sandoz), and rocuronium (Lot 8Y 011; Maruishi Pharmaceutical. Co., Ltd) were prepared as solutions with concentrations of 0.05 mg/mL, 5 mg/mL, and 10 mg/mL without dilution, respectively, since they can be used as undiluted solutions. Each of the prepared test materials was passed through a 0.22-μm filter (Millex-GV PVDF filter unit, Lot R9CA04857; Merck Millipore Ltd), after which compatibility testing for each of the prepared test materials was performed. Nafamostat was combined with 1-3 target drugs, and a total of 15 compatibility tests were conducted. In the 2-drug compatibility tests, nafamostat was mixed with fentanyl, morphine, midazolam, dexmedetomidine, and rocuronium. In the 3-drug compatibility tests, nafamostat and one of the analgesics (fentanyl or morphine) were combined with a sedative (midazolam or dexmedetomidine) or rocuronium. In the 4-drug compatibility tests, nafamostat, an analgesic (fentanyl or morphine), and rocuronium were combined with a sedative (midazolam or dexmedetomidine).

The compatibility test was conducted by preparing 4 test solutions in which nafamostat and the target drugs were compounded in a turbidity-measuring vial at an equal volume ratio (1:1, 1:1:1, or 1:1:1:1) to a total volume of 12 mL. In addition, 1 mL of each target drug, including nafamostat, was prepared for pH measurement during each test. Since it was unlikely that nafamostat and the target drug would be mixed in an infusion bottle or syringe, the observation time was up to 3 hours, which allowed for evaluation of the possibility of mixing in the infusion route[10,15]. In the compatibility test, pH, turbidity, visual appearance, and the Tyndall effect were evaluated immediately after mixing and at 1 and 3 hours. pH and turbidity were measured by inverting the test solutions 10 times immediately before measurement. The test was conducted at room temperature (25 ± 1°C) and in a scattered light environment (400-500 lx).

pH was measured using a pH meter (LAQUA act D72, Horiba Ltd.), in accordance with the Japanese Pharmacopoeia, 17th edition. Turbidity was measured using a turbidimeter (TurbiDirect TB300IR, Tintometer GmbH) and a method based on the scattered light measurement method. Three consecutive measurements of turbidity were made for each test solution in each time period. In

addition, 1 nafamostat reagent was used as a standard for the turbidity value. The measurable range of the measuring instrument was 0.01-1,100 nephelometric turbidity units (NTU). If measured values were below or above the quantitation limit, then the sample was analyzed as 0.01 NTU or 1,100 NTU, and it was specified that the limit of quantification was included. If all 4 compounded samples were below or above the detection limit, then the values were specified as <0.01 NTU and >1,100 NTU, respectively.

Visual inspection was performed against both a white and a black background with unaided eyes at a light intensity of 2,000-3,750 lx under a white light source, as suggested by the Japanese Pharmacopoeia, 17th edition. The Tyndall effect was observed in the dark with a red laser pointer (PR500-RC, 635 nm, maximum output 1 mW or less, Canon Marketing Japan Co., Ltd.). The laser was applied from the bottom of the turbidity measuring vial, and visual confirmation of the laser was defined as presence of the Tyndall effect.

Physical incompatibilities were defined as gross precipitation, cloudiness, appearance of the Tyndall effect, or a turbidity change of ≥0.5 NTU based on nafamostat[16–18].

Results

The pH values (mean ± standard deviation) of the test materials before the compatibility tests were as follows: nafamostat, 3.13 ± 0.03 (n = 15); fentanyl, 4.24 ± 0.08 (n = 6); morphine, 3.59 ± 0.03 (n = 6); midazolam, 3.34 ± 0.04 (n = 5); dexmedetomidine, 4.36 ± 0.25 (n = 5); and rocuronium, 2.97 ± 0.03 (n = 7). The turbidity value of nafamostat was <0.01 NTU (n = 1). The results of the all-compatibility tests are shown in **Table 1**. The highest pH was the combination of nafamostat, fentanyl, and dexmedetomidine (3.39 ± 0.01), 3 hours after mixing. The lowest pH was the combination of nafamostat and rocuronium (3.01 ± 0.01), 3 hours after mixing. The highest turbidity was the combinations of nafamostat and morphine and nafamostat, fentanyl, and midazolam (both 0.03 ± 0.03 NTU), immediately after mixing. After its preparation as an admixture, nafamostat was compatible with all the drugs or all combinations of drugs until 3 hours.

Discussion

This study evaluated the combination of nafamostat with analgesics, sedatives, and muscle relaxants that may need to be administered through the same infusion route for mechanical ventilation support during ECMO for COVID-19 patients. There were no physical incompatibilities in the combinations of nafamostat with the analgesics, sedatives, and muscle relaxants tested in this study. Therefore, this study is useful for those considering administration of combinations of these drugs through the same infusion route.

Analgesics and sedatives are often administered continuously to manage pain, restlessness, and delirium in patients under mechanical ventilation support during ECMO. Although fentanyl is recommended for use as an analgesic in the ICU[14], it is associated with a lower survival rate because of sequestration within the ECMO cycle[19]. Therefore, morphine is more likely to be selected for patients under ECMO support. Furthermore, *Clinical Management Of Patients with COVID-19: A Guide for Front-Line Healthcare Workers* (version 2.1) states that use of muscle relaxants may be considered for excessive spontaneous breathing efforts[20]. The use of muscle relaxants requires administration of analgesics and sedatives. Analgesics, sedatives, and muscle relaxants are often combined and administered through the same route in the ICU of our hospital, and other hospitals might use similar administration methods. Therefore, the muscle relaxant also underwent a 4-drug compatibility test.

The American Society of Health-System Pharmacists cautions that drug compatibility information should not be misinterpreted as applying to more than two specific agents under the study conditions[21]. In addition, existing compatibility studies of nafamostat with midazolam and fentanyl were conducted at nafamostat concentrations of 50 mg/1,000 mL and 10 mg/500 mL, respectively, which are lower than those used for COVID-19[12]. The compatibility tests of midazolam and fentanyl and 3 or more agents were carried out at a high nafamostat concentration (10 mg/mL). This study was the first to examine the compatibility of nafamostat with morphine, dexmedetomidine, and rocuronium. The results demonstrated a reduced risk of drug incompatibility during clinical management of COVID-19.

There were no combinations of physical incompatibilities in this study. In a previous study, nafamostat dissolved in water for administration as an injection (10 mg/mL) had a cloudy appearance above a pH of 10.06[22]. In this study, the combination of nafamostat, fentanyl, and dexmedetomidine had the highest pH (3.39 ± 0.01; 3 hours after mixing). Therefore, the present results for pH evaluation are consistent with those of the previous study, as the pH values for the drug combinations containing nafamostat were below 10.06.

Table 1 Physical compatibility tests of nafamostat with analgesics, sedatives, and muscle relaxants

	Combination of the test drugs				Immediately	1 hour	3 hours
Two-drug compatibility tests	Nafamostat	Fentanyl		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 60 mg/6 mL[a)]	0.3 mg/6 mL		Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Terumo		pH	3.31 ± 0.02	3.33 ± 0.03	3.31 ± 0.01
	pH 3.14	4.18		Turbidity (NTU)	<0.01	<0.01	<0.01
	Nafamostat	Morphine		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 60 mg/6 mL[a)]	12 mg/6 mL[b)]		Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Shionogi Pharma		pH	3.27 ± 0.01	3.29 ± 0.03	3.30 ± 0.01
	pH 3.15	3.56		Turbidity (NTU)	0.03 ± 0.03[c)]	0.03 ± 0.02[c)]	0.02 ± 0.02[c)]
	Nafamostat	Rocuronium		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 60 mg/6 mL[a)]	60 mg/6 mL		Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Maruishi		pH	3.03 ± 0.01	3.02 ± 0.02	3.01 ± 0.01
	pH 3.17	2.98		Turbidity (NTU)	<0.01	<0.01	<0.01
	Nafamostat	Midazolam		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 60 mg/6 mL[a)]	30 mg/6 mL		Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Sandoz		pH	3.21 ± 0.02	3.25 ± 0.01	3.25 ± 0.01
	pH 3.16	3.36		Turbidity (NTU)	<0.01	<0.01	<0.01
	Nafamostat	Dexmedetomidine		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 60 mg/6 mL[a)]	24 μg/6 mL[b)]		Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Sandoz		pH	3.28 ± 0.02	3.30 ± 0.01	3.29 ± 0.01
	pH 3.14	4.35		Turbidity (NTU)	<0.01	<0.01	<0.01
Three-drug compatibility tests	Nafamostat	Fentanyl	Rocuronium	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 40 mg/4 mL[a)]	0.2 mg/4 mL	40 mg/4 mL	Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Terumo	Maruishi	pH	3.04 ± 0.01	3.05 ± 0.01	3.01 ± 0.02
	pH 3.09	4.24	2.97	Turbidity (NTU)	<0.01	<0.01	0.01 ± 0.01[c)]
	Nafamostat	Fentanyl	Midazolam	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 40 mg/4 mL[a)]	0.2 mg/4 mL	20 mg/4 mL	Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Terumo	Sandoz	pH	3.35 ± 0.02	3.36 ± 0.03	3.35 ± 0.02
	pH 3.19	4.16	3.39	Turbidity (NTU)	0.03 ± 0.03[c)]	0.02 ± 0.01[c)]	0.02 ± 0.01[c)]
	Nafamostat	Fentanyl	Dexmedetomidine	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 40 mg/4 mL[a)]	0.2 mg/4 mL	16 μg/4 mL[b)]	Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Terumo	Sandoz	pH	3.38 ± 0.01	3.38 ± 0.01	3.39 ± 0.01
	pH 3.09	4.21	4.26	Turbidity (NTU)	<0.01	0.01 ± 0.01[c)]	<0.01
	Nafamostat	Morphine	Rocuronium	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc 40 mg/4 mL[a)]	8 mg/4 mL[b)]	40 mg/4 mL	Tyndall	None	None	None
	Mfr Asahi Kasei Pharma	Shionogi Pharma	Maruishi	pH	3.06 ± 0.01	3.06 ± 0.02	3.09 ± 0.01
	pH 3.17	3.63	3.00	Turbidity (NTU)	<0.01	<0.01	<0.01

Table 1 Physical compatibility tests of nafamostat with analgesics, sedatives, and muscle relaxants (continued)

		Combination of the test drugs					Immediately	1 hour	3 hours
		Nafamostat	Morphine	Midazolam		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	40 mg/4 mL[a)]	8 mg/4 mL[b)]	20 mg/4 mL		Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Shionogi Pharma	Sandoz		pH	3.32 ± 0.02	3.29 ± 0.02	3.28 ± 0.02
	pH	3.11	3.61	3.32		Turbidity (NTU)	<0.01	0.02 ± 0.01[c)]	0.02 ± 0.01[c)]
		Nafamostat	Morphine	Dexmedetomidine		Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	40 mg/4 mL[a)]	8 mg/4 mL[b)]	16 μg/4 mL[b)]		Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Shionogi Pharma	Sandoz		pH	3.33 ± 0.01	3.33 ± 0.02	3.35 ± 0.02
	pH	3.09	3.57	4.07		Turbidity (NTU)	<0.01	<0.01	<0.01
Four-drug compatibility tests		Nafamostat	Fentanyl	Rocuronium	Midazolam	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	30 mg/3 mL[a)]	0.15 mg/3 mL	30 mg/3 mL	15 mg/3 mL	Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Terumo	Maruishi	Sandoz	pH	3.06 ± 0.02	3.04 ± 0.01	3.06 ± 0.02
	pH	3.11	4.38	2.92	3.29	Turbidity (NTU)	<0.01	0.01 ± 0.00[c)]	0.02 ± 0.02[c)]
		Nafamostat	Fentanyl	Rocuronium	Dexmedetomidine	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	30 mg/3 mL[a)]	0.15 mg/3 mL	30 mg/3 mL	12 μg/3 mL[b)]	Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Terumo	Maruishi	Sandoz	pH	3.04 ± 0.02	3.03 ± 0.01	3.04 ± 0.03
	pH	3.09	4.27	2.93	4.75	Turbidity (NTU)	<0.01	<0.01	0.01 ± 0.01[c)]
		Nafamostat	Morphine	Rocuronium	Midazolam	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	30 mg/3 mL[a)]	6 mg/3 mL[b)]	30 mg/3 mL	15 mg/3 mL	Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Shionogi Pharma	Maruishi	Sandoz	pH	3.09 ± 0.02	3.14 ± 0.01	3.11 ± 0.01
	pH	3.14	3.57	3.00	3.35	Turbidity (NTU)	<0.01	<0.01	<0.01
		Nafamostat	Morphine	Rocuronium	Dexmedetomidine	Visual	Colorless and clear	Colorless and clear	Colorless and clear
	Conc	30 mg/3 mL[a)]	6 mg/3 mL[b)]	30 mg/3 mL	12 μg/3 mL[b)]	Tyndall	None	None	None
	Mfr	Asahi Kasei Pharma	Shionogi Pharma	Maruishi	Sandoz	pH	3.09 ± 0.01	3.07 ± 0.02	3.06 ± 0.01
	pH	3.15	3.62	3.00	4.39	Turbidity (NTU)	<0.01	<0.01	<0.01

a) Prepared in 5% dextrose injection b) Prepared in 0.9% sodium chloride injection c) Including less than the quantification limit

Conc: Concentration of the test drug, Mfr: Manufacturer of the test drug, NTU: Nephelometric turbidity unit

This study had some limitations. Chemical compatibility tests, such as stability testing, were not conducted. Nafamostat is known to undergo degradation after mixing with sodium bisulfite, which is used as a stabilizer during injectable preparation[10,23]. Although there was no injectable drug containing sodium bisulfite among the tested drugs, there may have been instabilities while combining the drugs in this study. However, a recent systematic review found that data on physical and/or chemical compatibility were available for only 41 of the possible 820 two-drug combinations (54%) that are commonly used in the ICU, and that data on chemical compatibility were available for only 9% of the possible combinations[24]. Information on compatibility tests for selecting an infusion line in the ICU area is limited. Although this study evaluated only physical combination changes, our results may have high clinical significance.

In conclusion, our study showed that there were no physical incompatibilities when nafamostat was combined with the tested analgesics, sedatives, and muscle relaxants. Therefore, infusion line combinations of nafamostat with the sedatives, analgesics, and muscle relaxants examined in this study are safe. Future studies of chemical compatibility are warranted. Moreover, if new treatment options for COVID-19 are reported, then additional drug compatibility tests should be performed to ensure effective clinical management for patients with COVID-19.

Acknowledgements: We thank Professor Akio Yanagida, Department of Biomedical Analysis, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, for his advice on the analytical methods for the compatibility test. This work was supported by JSPS KAKENHI, Grant Number 18K16547. The funders had no role in the execution of this study or interpretation of the results.

Conflict of Interest: The authors declare no conflicts of interest.

References

1. Takemoto Y, Tanaka S, Tanabe J, Nakamura Y, Kohama A, Shibata S. Studies on the effects of primary therapy for DIC following circulatory arrest. Am J Hematol. 1986 Apr;21(4):377−82.
2. Minakata D, Fujiwara SI, Ikeda T, et al. Comparison of gabexate mesilate and nafamostat mesilate for disseminated intravascular coagulation associated with hematological malignancies. Int J Hematol. 2019 Feb;109(2):141−6.
3. Hoffmann M, Schroeder S, Kleine-Weber H, Muller MA, Drosten C, Pohlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: New treatment option for COVID-19. antimicrob agents chemother [Internet]. 2020 May 21; 64(6):e00754-20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32312781
4. Jang S, Rhee JY. Three cases of treatment with Nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. Int J Infect Dis [Internet]. 2020 Jul;96:500−2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32470602
5. Doi K, Ikeda M, Hayase N, Moriya K, Morimura N. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. Crit Care. 2020 Jul 3;24(1):392.
6. Zhan WQ, Li MD, Xu M, Lu YB. Successful treatment of COVID-19 using extracorporeal membrane oxygenation, a case report. Eur Rev Med Pharmacol Sci. 2020 Mar;24(6): 3385−9.
7. Taniguchi H, Ogawa F, Honzawa H, et al. Veno-venous extracorporeal membrane oxygenation for severe pneumonia: COVID-19 case in Japan. Acute Med Surg [Internet]. 2020 Jan-Dec;7(1):e509. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32313662
8. Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med. 2020;8(5):518−26.
9. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020 May;18(5):1023−6.
10. Saito S. Chushayaku haigouhenka de-ta kensaku 2009 [Datebase on injectable drugs 2009]: Yakujishinpousya Publishing; 2009. p. 1−199. Japanese.
11. Fukushima H, Mori S. Chushayaku no haigouhenka [Incompatibilities of parenteral injections]: F Copint・Fuji syoin Publishing; 2002. p. 1−3098. Japanese.
12. Ishimoto K. Chusyayaku cyouzai kansa manyuaru 2018 [Injectable drug audit manual 2018]: Elsevier Japan Publishing; 2018. p. 1−719. Japanese.
13. American Society of Health-System Pharmacists. Handbook on injectable drugs: American Society of Health-System Pharmacists, Maryland: 2017. p. 1−1280.
14. Committee for the development of Japanese guidelines for the management of Pain, Agitation, and Delirium in intensive care unit, Japanese Society of Intensive Care Medicine. Shuchu chiryo ryoiki niokeru itami・fuon・semmo kanri no genjo chosa (2019 nen) [Nationwide survey of Pain, Agitation, and Delirium management in Japanese intensive care setting, 2019]. Nippon Shuchu Chiryo Igakkai Zasshi [J Jpn Soc Intensive Care Med] [Internet]. 2020;27(2):150−8. Available from: http://search.jamas.or.jp/link/ui/U325230016 Japanese.
15. Abe S, Matsumoto S, Kobayashi G, et al. ICU niokeru chushayaku haigou henka hayamihyo no sakusei to sono yuyousei no kento [Preparation of quick reference table on incompatibilities of injections for use in the ICU and investigation of the usefulness of this table]. Iyakuhin Johogaku [Jpn J Drug Inform] [Internet]. 2012;14(2):75−81. Available from: http://search.jamas.or.jp/link/ui/2012336626 Japanese.
16. Thabit AK, Hamada Y, Nicolau DP. Physical compatibility of ceftolozane-tazobactam with selected i.v. drugs during simulated Y-site administration. Am J Health Syst Pharm [Internet]. 2017 Jan 1;74(1):e47−54. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28007721
17. Kidd JM, Avery LM, Asempa TE, Nicolau DP, Kuti JL. Physical compatibility of meropenem and vaborbactam with select intravenous drugs during simulated y-site ad-

ministration. Clin Ther [Internet]. 2018 Feb;40(2):261–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29290374
18. Trissel LA, Bready BB. Turbidimetric assessment of the compatibility of taxol with selected other drugs during simulated Y-site injection. Am J Hosp Pharm. 1992 Jul;49(7):1716–9.
19. Shekar K, Roberts JA, McDonald CI, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care. 2012 Oct 15;16(5):R194.
20. Minister of Health, Labour and Welfare. Clinical management of patients with COVID-19: A guide for front-line healthcare workers (Version 2.1) [Internet]. 2020 Jul 3 [cited 2020 Sep 11]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00111.html
21. American Society of Health-SystemPharmacists (ASHP). ASHP's Interactive Handbook on INJECTABLE DRUGS [Internet]. 2020 [cited 2020 Mar 21]. Available from: https://www.interactivehandbook.com/Authentication/Authentication.aspx
22. Asahi Kasei Pharma Corporation. Iyakuhin intabyu fomu, nafamosutattomeshirusanen chushayo 100 mg [The interview form of nafamostat mesylate 5th edition]. 2018 Dec. Japanese.
23. Takasu Y, Yoshida M, Shimizu K, Asahara K, Tange M, Uchida T. Prediction of the stability of octreotide in a mixed infusion. Chem Pharm Bull (Tokyo). 2014;62(4):316–21.
24. Kanji S, Lam J, Johanson C, et al. Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. Crit Care Med [Internet]. 2010 Sep;38(9):1890–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20562698

(Received, October 4, 2020)
(Accepted, February 3, 2021)
(J-STAGE Advance Publication, March 9, 2021)