Physical compatibility of nafamostat with analgesics, sedatives, and muscle relaxants for coronavirus disease treatment

Running head: Nafamostat compatibility in COVID-19

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Abstract

Background: Severe coronavirus disease (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 four test solutions wherein 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 $\geq 0.5$ nephelometric turbidity unit (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.

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

The first case of coronavirus disease (COVID-19) was reported in the People's Republic of China in December 2019, and it subsequently spread to many countries worldwide, including Japan. Nafamostat is a therapeutic agent for pancreatitis and disseminated intravascular coagulation. Continuous administration of nafamostat at a dose of 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, and has recently been reported as a therapeutic agent for COVID-19.

Severe COVID-19 patients require mechanical ventilation during extracorporeal membrane oxygenation (ECMO) support, and it is assumed that there will be a need for continuous injections of drugs such as analgesics, sedatives, and muscle relaxants. COVID-19 causes an increased risk of thrombosis, and the International Society on Thrombosis and Hemostasis (ISTH) recommends prophylaxis with heparin for patients requiring hospitalization. Nafamostat treatment for severe COVID-19 is thus likely to be 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 can be employed 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.

Severe COVID-19 patients 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. Compatibility tests between nafamostat and analgesics, sedatives, and muscle relaxants have not been carried out with morphine, dexmedetomidine, or rocuronium. Additionally, only a few multi-drug compatibility tests, wherein three 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 one, the ethics committee of Nippon Medical School Tama Nagayama Hospital deemed that ethical review was not necessary. 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 that were 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\textsuperscript{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 5\% glucose solution (Lot 9J96P; 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 8Y011; 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); subsequently, the compatibility test 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 two-drug compatibility tests, nafamostat was mixed with fentanyl, morphine, midazolam, dexmedetomidine, and rocuronium. In the three-drug compatibility tests, nafamostat and one of the analgesics (fentanyl or morphine) were combined with either a sedative (midazolam or dexmedetomidine) or rocuronium. In the four-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 four 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 the evaluation of the possibility of mixing in the infusion route. 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.) according to the Japanese Pharmacopoeia, 17th edition. Turbidity was measured using a turbidimeter (TurbiDirect TB300IR, Tintometer GmbH) based on the scattered light measurement method. Three consecutive measurements of turbidity were made for each test solution in each time period. In addition, one 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 the 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 four 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 according to the Japanese Pharmacopoeia, 17th edition. The Tyndall effect was observed
in the dark using 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 value ± 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. Nafamostat was compatible with all the drugs or all combinations of drugs until 3 hours after its preparation as an admixture.

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 in 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 considering the administration of a combination 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. Fentanyl is recommended for use as an analgesic in the ICU14. However, fentanyl has been reported to have a reduced survival rate due to sequestration within the ECMO cycle19. Therefore, it is assumed that morphine may be selected in patients under ECMO support. Furthermore, clinical management of patients with COVID-19: a guide for front-
line healthcare workers (version 2.1) states that the use of muscle relaxants may be considered for excessive spontaneous breathing efforts\(^\text{20}\). The use of muscle relaxants requires the 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 there is a possibility that similar administration methods are being implemented at other hospitals. 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\(^\text{21}\). In addition, existing compatibility studies of nafamostat with midazolam and fentanyl were conducted at nafamostat concentrations of 50 mg/1000 mL and 10 mg/500 mL, respectively, which are lower than those used for COVID-19\(^\text{12}\). The compatibility tests of midazolam and fentanyl and three or more agents were carried out at a high concentration of nafamostat (10 mg/mL). This study was the first to examine the compatibility of nafamostat with morphine, dexmedetomidine, and rocuronium. Therefore, this study demonstrated a reduced risk of drug incompatibility during the clinical management of COVID-19.

There were no combinations of physical incompatibilities in this study. In a
previous study, nafamostat was dissolved in water for administration as an injection (10 mg/mL), and showed a cloudy appearance above a pH of 10.06\textsuperscript{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 results of this study were considered consistent with those of the previous study in terms of pH evaluation, as the pH of the drug combinations containing nafamostat was below 10.06.

This study had some limitations. In this study, chemical compatibility tests such as stability were not conducted. Nafamostat is known to undergo degradation after mixing with sodium bisulfite, which is used as a stabilizer during injectable preparation\textsuperscript{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, according to a recent systematic review, the data of 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 the data of chemical compatibility were available for only 9\% of the possible combinations\textsuperscript{24}. Information regarding compatibility tests for selecting the infusion line in the ICU area is still lacking. 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 in the combination of nafamostat with the tested analgesics, sedatives, and muscle relaxants. Therefore, the infusion line combinations of nafamostat with the sedatives, analgesics, and muscle relaxants examined this study could be safely carried out. In the future, conducting chemical compatibility tests is warranted. Moreover, if new treatment options for COVID-19 are reported in literature, then additional drug compatibility tests should be performed to ensure effective clinical management for patients with COVID-19.
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Conflict of Interest

The authors declare no conflicts of interest.
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<sup>1.9</sup> | Tyndall | None | None | None |
| Mfr: Asahi Kasei Pharma | pH: 3.14 | 3.31 ± 0.02 | 3.33 ± 0.03 | 3.31 ± 0.01 |
| & Terumo | Turbidity(NTU): < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| Conc: 0.3 mg/6 mL<sup>10</sup> | | | | |
| Mfr: Maruishi | | | | |
| Conc: 12 mg/6 mL<sup>11</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Shionogi Pharma | Tyndall | None | None | None |
| Conc: 3.65 | pH: 3.27 ± 0.01 | 3.29 ± 0.03 | 3.30 ± 0.01 | 3.30 ± 0.01 |
| & Morphone | Turbidity(NTU): 0.03 ± 0.02<sup>12</sup> | 0.03 ± 0.02<sup>12</sup> | 0.02 ± 0.02<sup>12</sup> | 0.02 ± 0.02<sup>12</sup> |
| Conc: 60 mg/6 mL<sup>12</sup> | | | | |
| Mfr: Asahi Kasei Pharma | | | | |
| Conc: 3.19 | | | | |
| Conc: 30 mg/6 mL<sup>13</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Sandoz | Tyndall | None | None | None |
| Conc: 3.36 | pH: 3.21 ± 0.02 | 3.25 ± 0.01 | 3.25 ± 0.01 | 3.25 ± 0.01 |
| & Midazolam | Turbidity(NTU): < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| Conc: 24 μg/6 mL<sup>14</sup> | | | | |
| Mfr: Maruishi | | | | |
| Conc: 4.35 | | | | |
| Conc: 8 mg/4 mL<sup>15</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Sandoz | Tyndall | None | None | None |
| Conc: 4.21 | pH: 3.38 ± 0.01 | 3.38 ± 0.01 | 3.39 ± 0.01 | 3.39 ± 0.01 |
| & Dexmedetomidine | Turbidity(NTU): < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| Conc: 16 μg/4 mL<sup>16</sup> | | | | |
| Mfr: Sandoz | | | | |
| Conc: 4.26 | | | | |
| Conc: 8 mg/4 mL<sup>17</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Shionogi Pharma | Tyndall | None | None | None |
| Conc: 3.63 | pH: 3.32 ± 0.02 | 3.29 ± 0.03 | 3.32 ± 0.02 | 3.32 ± 0.02 |
| & Rocuronium | Turbidity(NTU): 0.01 ± 0.01<sup>18</sup> | 0.02 ± 0.01<sup>18</sup> | 0.02 ± 0.01<sup>18</sup> | 0.02 ± 0.01<sup>18</sup> |
| Conc: 40 mg/4 mL<sup>18</sup> | | | | |
| Mfr: Maruishi | | | | |
| Conc: 3.17 | | | | |
| Conc: 8 mg/4 mL<sup>19</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Sandoz | Tyndall | None | None | None |
| Conc: 3.61 | pH: 3.33 ± 0.01 | 3.33 ± 0.02 | 3.35 ± 0.02 | 3.35 ± 0.02 |
| & Midazolam | Turbidity(NTU): < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| Conc: 16 μg/4 mL<sup>20</sup> | | | | |
| Mfr: Sandoz | | | | |
| Conc: 4.07 | | | | |
| Conc: 8 mg/4 mL<sup>21</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Shionogi Pharma | Tyndall | None | None | None |
| Conc: 3.57 | pH: 3.24 ± 0.02 | 3.24 ± 0.03 | 3.26 ± 0.03 | 3.26 ± 0.03 |
| & Morphine | Turbidity(NTU): 0.02 ± 0.02<sup>22</sup> | 0.02 ± 0.02<sup>22</sup> | 0.02 ± 0.02<sup>22</sup> | 0.02 ± 0.02<sup>22</sup> |
| Conc: 30 mg/3 mL<sup>22</sup> | | | | |
| Mfr: Shionogi Pharma | | | | |
| Conc: 3.11 | | | | |
| Conc: 6 mg/3 mL<sup>23</sup> | Visual | Colorless and clear | Colorless and clear | Colorless and clear |
| Mfr: Maruishi | Tyndall | None | None | None |
| Conc: 3.57 | pH: 3.09 ± 0.01 | 3.07 ± 0.02 | 3.06 ± 0.01 | 3.06 ± 0.01 |
| & Midazolam | Turbidity(NTU): < 0.01 | < 0.01 | < 0.01 | < 0.01 |
| Conc: 12 μg/3 mL<sup>24</sup> | | | | |
| Mfr: Sandoz | | | | |
| Conc: 4.39 | | | | |
| 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 |