Nafamostat mesylate (NM) is a synthetic serine protease inhibitor originally developed as a therapeutic drug for pancreatitis. As it has an inhibitory action on platelet aggregation and coagulation factors, NM has commonly been used as an anticoagulant in continual renal replacement therapies. However, NM use is associated with adverse effects including hyperkalemia, agranulocytosis, and anaphylaxis. Here, we describe 4 cases of NM-induced anaphylaxis and review the adverse drug reactions caused by NM in the Korea Institute of Drug Safety-Korea Adverse Event Reporting System (KIDS-KAERS). This study was approved by the Institutional Review Board of the Hallym University Sacred Heart Hospital (No. 2020-05-012).

Patient 1 was a 75-year-old female admitted to this hospital for the treatment of left malleolar bursitis. She had been on hemodialysis for 10 years. As she had to maintain ant-platelet agents during the surgery due to underlying atrial fibrillation with ischemic heart diseases, NM was used to reduce bleeding risk from the surgical wound. During the sixth hemodialysis session after the surgery, she complained of itching, which subsided after a pheniramine injection. During the next hemodialysis session, sudden cardiac arrest occurred following the complaint of itching and urticaria. Based on her symptoms and elevated tryptase level (44.1 µg/mL), anaphylaxis was strongly suggested. Dialysis was restarted the next day without NM, and there were no further complications. We further collected information regarding 3 cases of NM-induced anaphylaxis having similar clinical manifestations (Table 1). In these cases, we performed NM skin tests and basophil activation tests to differentiate between anaphylaxis and dialyzer reactions. As shown in Table 1, 3 patients were positive in the skin prick test or intradermal test. Patient 1 was negative in the skin prick test and refused to undergo the intradermal test. All patients had positivity to basophil activation tests to NM (Supplementary Fig. S1).

Given these unique cases, we reviewed the pharmacovigilance data for NM collected from the KIDS-KAERS database of the Korea Institute of Drug Safety and Risk Management (Ministry of Food and Drug Safety) from 2007 to 2017. A total of 1,559 adverse drug reactions were collected, and 1,102 cases were assessed as certain (n = 19), probable/likely (n = 341) or possible (n = 742) according to the World Allergy Organization diagnostic criteria. Particularly, in the cases where NM was used as an anticoagulant during renal replacement therapy in patients with chronic kidney disease, 53 cases were detected, of which 4 were originally reported as anaphylaxis, and 4 were newly reassessed as anaphylaxis. The most common manifestation was cutaneous (29.8%), followed by gastrointestinal and cardiovascular (22.8% and 12.3%, respectively, Supplementary Table S1). Based on national...
Anaphylaxis Due to Nafamostat Mesylate

Table 1. Patient characteristics

| Patient | Age (yr) | Sex | Clinical manifestations | Onset time (min) | Prior exposure | Skin test | Basophil activation test | Atopy | Total IgE (IU/L) | Allergic disease | Indication for NM use |
|---------|---------|-----|-------------------------|------------------|----------------|-----------|--------------------------|-------|-----------------|-------------------|-----------------------|
| Patient 1 | 75     | F   | Cardiac arrest          | 50               | +             | SPT (−) IDT (ND) | +       | +                | 2,500             | Asthma           | Incision and drainage of left. malleolar bursitis |
| Patient 2 | 65     | F   | Itching, urticaria, chest discomfort, dyspnea | 5       | +             | SPT (−) IDT (−, 1 mg/mL) | +       | –                | 93.1              | None              | Hematoma          |
| Patient 3 | 84     | F   | Itching, mental change, hypotension | 5       | +             | SPT (−) IDT (−, 1 mg/mL) | +       | –                | 224               | None              | SAH                |
| Patient 4 | 69     | F   | Itching, urticaria, chest discomfort, dyspnea | 5       | +             | SPT (+, 5 mg/mL) IDT (ND) | +       | +                | 230               | None              | Cataract operation |

IgE, immunoglobulin E; F, female; IDT, intradermal test; ND, not done; NM, nafamostat mesylate; SAH, subarachnoid hemorrhage; SPT, skin prick test.

In conclusion, clinical suspicion is important for diagnosing an allergic reaction caused by NM. Patients receiving NM with hemorrhagic complications during blood purification should be carefully monitored for anaphylaxis even after several uneventful administrations of this drug. A skin test or basophil activation test is useful for confirming the diagnosis.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1
Clinical manifestations of ADRs to nafamostat mesylate in the Korean pharmacovigilance system (n = 33 patients, 53 reports)

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Supplementary Fig. S1
Expression of CD63 and CD203c on basophils of patients after treatment with 10^{-5}, 10^{-3}, and 10^{-1} mg/mL nafamostat mesylate. The stimulation index is the percentage of basophils activated by the drug divided by the percentage of activated basophils in the negative control.

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