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Letter to the Editor

Fatal anaphylaxis Due to Nafamostat Mesylate During Hemodialysis

Joo-Hee Kim,[1*] **Ji Young Park**,[1] **Seung Hun Jang**,[1] **Jwa-Kyung Kim**,[2] **Young Rim Song**,[2] **Hyung Seok Lee**,[2] **Sung Gyun Kim** [2]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea
[2]Division of Nephrology, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

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Correspondence to
Joo-Hee Kim, MD, PhD
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea.
Tel: +82-31-380-3719
Fax: +82-31-380-3973
E-mail: luxjhee@gmail.com
luxjhee@hallym.or.kr

ORCID iDs
Joo-Hee Kim
https://orcid.org/0000-0002-1572-5149
Ji Young Park
https://orcid.org/0000-0002-6533-4656
Seung Hun Jang
https://orcid.org/0000-0001-5457-5780
Jwa-Kyung Kim
https://orcid.org/0000-0002-7726-2143
Young Rim Song
https://orcid.org/0000-0002-0416-4745
Hyung Seok Lee
https://orcid.org/0000-0001-6380-9243

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.[1] However, NM use is associated with adverse effects including hyperkalemia, agranulocytosis, and anaphylaxis.[2,3] 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)[4,5] 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

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.

Sung Gyun Kim
https://orcid.org/0000-0002-5034-0527

Disclosure

There are no financial or other issues that might lead to conflict of interest.

pharmacovigilance data, anaphylaxis accounts for 15% (8/53) of all adverse reactions to NM when it is used as an anticoagulant during blood purification, suggesting that the overall adverse reactions to NM are low but that severe allergic reactions can occur during dialysis.

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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