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Case Report

Cardiac arrest caused by nafamostat mesilate

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Abstract

A 65-year-old man was transferred from the Department of Vascular Surgery to Nephrology because of cardiac arrest during hemodialysis. He underwent incision and drainage for treatment of a buttock abscess. Nafamostat mesilate was used as an anticoagulant for hemodialysis to address bleeding from the incision and drainage site. Sudden cardiac arrest occurred after 15 minutes of dialysis. The patient was treated in the intensive care unit for 5 days. Continuous veno-venous hemodiafiltration was started without any anticoagulant in the intensive care unit. Conventional hemodialysis was reinitiated, and nafamostat mesilate was used again because of a small amount of continued bleeding. Ten minutes after hemodialysis, the patient complained of anaphylactic signs and symptoms such as dyspnea, hypotension, and facial swelling. Epinephrine, dexamethasone, and pheniramin were injected under the suspicion of anaphylactic shock, and the patient recovered. Total immunoglobulin E titer was high, and skin prick test revealed weak positivity for nafamostat mesilate. We first report a case of anaphylactic shock caused by nafamostat mesilate in Korea.

Introduction

Generally, heparin is used to control circuit coagulation during hemodialysis; however, it does affect the systemic blood coagulation. For patients at high risk of bleeding, alternative modalities, such as saline flushes, regional citrate anticoagulation, prostacyclin, danaparoid, argatroban (direct thrombin inhibitor), and lepirudin (recombinant hirudin), are available [1]. Nafamostat mesilate is a serine protease-inhibitor discovered by Fujii and Hitomi [2]. It has been studied for its anticoagulant effect and used clinically in hemodialysis since 1989 [3].

Nafamostat mesilate inhibits various enzyme systems, such as coagulation and fibrinolytic systems (thrombin, Xa, and XIIa), the kallikrein–kinin system, the complement system, and pancreatic proteases. Because it is not absorbed by the anion exchange resin, it does not affect bone and lipid metabolism [4]. It has a biological half-life of 8 minutes or less, and approximately 40% of the molecule is dialyzed through the dialyzer [5]. In addition, its anticoagulant effect is strictly limited to the extracorporeal circuit [5]. Because of the characteristics described previously, it has been used in patients who are at high risk of bleeding and those with heparin-induced thrombocytopenia.

However, several allergic reactions caused by nafamostat mesilate have been reported in Japan. Most allergic reactions reported that there were mild symptoms, such as abdominal pain, nausea, vomiting, anorexia, myalgia, and arthralgia. More serious symptoms such as severe hypotension and dyspnea, however, have also been reported in several cases. There have

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been no previous case reports of allergic reactions caused by nafamostat mesilate in Korea. Therefore, we would like to present a case of anaphylactic shock caused by nafamostat mesilate.

Case report

A 65-year-old man was admitted to this hospital in March 2015 to establish new vascular access for dialysis. He was diagnosed with hypertension and diabetes in 2004 and underwent lower anterior resection for rectal cancer followed by radiotherapy in the same year. He started maintenance hemodialysis due to diabetic nephropathy in 2010. He was dialyzed through a permanent catheter placed in the right jugular vein at the time of admission. The Polyflux 14L (Polyarylethersulfone, Polyvinylpyrrolidone, Polyamide blend, Steam sterilized; Gambro, Lund, Sweden) was used as a dialyzer, and heparin was applied as an anticoagulant. He underwent incision and drainage for treatment of a buttock abscess after having received dialysis 4 times. After the second dialysis after the operation, nafamostat mesilate was used because of bleeding from the incision and drainage site. After initiating dialysis with nafamostat mesilate, the patient complained of bilateral eye congestion and buttock pain; sudden cardiac arrest occurred after 15 minutes of dialysis. Spontaneous circulation was restored after 7 minutes of cardiac massage. Laboratory results at that time were as follows: white blood cells 27.5 $\times$ 10^3/μL (eosinophil 0.1%), hemoglobin 9.9 g/dL, hematocrit 30.5%, platelets 296 $\times$ 10^3/μL, activated partial thromboplastin time 118.3 seconds, prothrombin time 13.2 seconds (international normalized ratio 1.26), serum creatinine 2.58 mg/dL, blood urea nitrogen 26.8 mg/dL, aspartate transaminase 35 U/L, alanine transaminase 20 U/L, total protein 4.8 g/dL, albumin 1.9 g/dL, Na 131 mmol/L, K 3.3 mmol/L, Cl 100 mmol/L, total CO_2 15 mmol/L, Ca 7.1 mg/dL, phosphate 2.9 mg/dL, glucose 297 mg/dL, C-reactive protein 4.77 mg/dL, and lactic dehydrogenase level of 317 IU/L (normal range, 100–450 IU/L). Arterial blood gas showed pH 7.263, pCO_2 48.6 mmHg, pO_2 153.1 mmHg, HCO_3 21.5 mmol/L, and O_2 saturation 98.7%. Echocardiography results were as follows: normal left ventricular systolic function, no regional wall motion abnormality, left ventricular hypertrophy, and relaxation abnormality.

The patient recovered consciousness after return of spontaneous circulation, but hypotension persisted. Norepinephrine was continuously infused for 2 days to maintain blood pressure, and continuous veno-venous hemodiafiltration was started without any anticoagulant because of constant bleeding from the site of the drained abscess on the buttock area. The patient was treated in the intensive care unit for 5 days, and there were no other complications during continuous veno-venous hemodiafiltration.

Conventional hemodialysis was reinitiated, and nafamostat mesilate was used again because of a small amount of continued bleeding on the buttock area. Ten minutes after hemodialysis, the patient complained of a sensation of heat on the buttock area, dyspnea, facial swelling, and congestion of both eyes. Blood pressure was 110/60 mmHg just before hemodialysis, but soon was unmeasurable, with only a weak pulse felt over the femoral artery. Intramuscular epinephrine, intravenous dexamethasone, and intravenous pheniramin were injected under the suspicion of anaphylactic shock, and the blood pressure recovered to 80/50 mmHg. Predialysis laboratory results were as follows: white blood cells 7.4 $\times$ 10^3/μL (eosinophil 9.6%), hemoglobin 10.0 g/dL, hematocrit 30.1%, and platelet count 65 $\times$ 10^3/μL. Serum creatinine was 2.18 mg/dL, blood urea nitrogen 23.0 mg/dL, aspartate transaminase 24 U/L, alanine transaminase 8 U/L, total protein 5.3 g/dL, albumin 2.3 g/dL, Na 137 mmol/L, K 4.3 mmol/L, Cl 102 mmol/L, total CO_2 23 mmol/L, and lactic dehydrogenase 206 IU/L.

Nafamostat mesilate was a suspected cause of the anaphylactic shock. A skin prick test and total immunoglobulin E (IgE) test were performed for evaluation of nafamostat mesilate allergy. We could not perform specific IgE testing because the test equipment was not available. Nafamostat mesilate allergy was ultimately diagnosed based on a weak positive result on skin prick test and elevation of total IgE. There were no additional events in subsequent hemodialysis runs without nafamostat mesilate. He underwent surgery to establish new vascular access and was subsequently discharged.

Discussion

Nafamostat mesilate is a serine protease inhibitor that inhibits various enzyme systems, such as coagulation and fibrinolytic systems (thrombin, Xa, and XIIa), the kallikrein–kinin system, the complement system, and pancreatic proteases. Nafamostat mesilate has 3 advantageous features compared to heparin. First, it does not affect systemic coagulation; second, it inhibits the complement system; and third, it has no lipolytic activity [4]. In addition, Chika et al [6] reported that nafamostat mesilate inhibited plasma bradykinin elevation and can prevent anaphylactic shock, which is induced by low-density lipoprotein apheresis with heparin. Therefore, the use of nafamostat mesilate has advantages over heparin if the patients are at high risk of bleeding. However, there have been several cases of allergic reactions to nafamostat mesilate. Yamazato et al [3] reported a patient who complained of severe abdominal pain and throat irritation during the sixth hemodialysis run using nafamostat mesilate; in that case, the drug lymphocyte stimulation test and specific IgE were positive. Akizawa [4] reported that 3 of 66 patients complained of anorexia, general lassitude, slight myalgia, and arthralgia during hemodialysis using nafamostat mesilate, and symptoms disappeared after the end of dialysis. Maruyama et al [5] described the first case of an anaphylactoid reaction caused by nafamostat mesilate. Their patient complained of nausea, vomiting, sweating, chest discomfort, and abdominal pain followed by shock. The drug lymphocyte stimulation test was positive for nafamostat mesilate, whereas specific IgE was negative in the reported case. Higuchi et al [7] reported a patient with hypotension that occurred during his ninth hemodialysis run using nafamostat mesilate. In that case, the drug lymphocyte stimulation test for nafamostat mesilate was positive, but specific IgE was negative. Shunsuke et al [8] reported a case of acquired allergic reaction to nafamostat mesilate during long-term maintenance of hemodialysis.

Similar to the case of Shunsuke et al [8], our patient had a history of nafamostat mesilate exposure at least 1 year before, but there were no previous adverse events. Cardiac arrest occurred during the first hemodialysis with nafamostat mesilate at our hospital. Unfortunately, the mechanism of nafamostat mesilate anaphylaxis remains unclear, as in the previously reported cases. Nagase et al [9] reported that the specific IgE antibody to nafamostat mesilate has high sensitivity to allergic reaction. We could not conclude the exact mechanism of nafamostat mesilate

anaphylaxis because specific IgE was not tested in our case. Nevertheless, elevated serum total IgE and weak positivity to skin prick test indirectly suggested that the main mechanism might be related to IgE-mediated allergic reaction.

In conclusion, various etiologies, such as cardiovascular disease, sepsis, air embolism, and membrane reaction, must be evaluated as potential causes of cardiac arrest during dialysis, and anaphylactic shock due to drug allergy should also be considered. Clinical suspicion is very important in diagnosing nafamostat mesilate allergy. If patients complain of unusual symptoms repeatedly during dialysis using nafamostat mesilate, it is important to check their allergy histories and to perform a skin prick test for nafamostat mesilate. Skin prick test is very useful because it is easy to perform and it provides results within few minutes. If an allergic reaction occurs, typical treatment for anaphylaxis including hydration, epinephrine, antihistamine, and steroid injection should be performed.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] Kim EY, Lee YK, Lee SM, Choi MJ, Song YR, Kim SJ, Park TJ, Kim SG, Oh J, Seo JW, Yoon JW, Koo JR, Kim HJ, Noh JW: Low-dose nafamostat mesilate in hemodialysis patients at high bleeding risk. *Korean J Nephrol* 30:61–66, 2011

[2] Fujii S, Hitomi Y: New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kallikrein and trypsin. *Biochim Biophys Acta* 661: 342–345, 1981

[3] Yamazato M, Mano R, Oshiro-Chinen S, Tomiyama N, Sakima A, Ishida A, Tana T, Tozawa M, Muratani H, Iseki K, Takishita S: Severe abdominal pain associated with allergic reaction to nafamostat mesilate in a chronic hemodialysis patient. *Intern Med* 41:864–866, 2002

[4] Akizawa T: Beneficial characteristics of protease inhibitor as an anticoagulant for extracorporeal circulation. *Rinsho Ketsueki* 31: 782–786, 1990

[5] Maruyama H, Miyakawa Y, Gejyo F, Arakawa M: Anaphylactoid reaction induced by nafamostat mesilate in a hemodialysis patient. *Nephron* 74:468–469, 1996

[6] Chika M, Tsutomu S, Minoru A, Satoru N, Kazuo K, Iwakazu K, Hirosi N, Tetsuzo A: Anaphyractoid reaction in LDL apheresis. *J Artif Organs* 23:533–536, 1994

[7] Higuchi N, Yamazaki H, Kikuchi H, Gejyo F: Anaphylactoid reaction induced by a protease inhibitor, nafamostat mesilate, following nine administrations in a hemodialysis patient. *Nephron* 86:400–401, 2000

[8] Shunsuke T, Masayoshi K, Hiromitsu Y, Akihiro Y, Ryoichi S, Yasuhiro S: A case of anaphylaxis induced by nafamostat mesilate in the long-term maintenance of hemodialysis. *J Nara Med Assoc* 48: 61–64, 1997

[9] Nagase K, Fukunaga K, Ohnishi K, Kusaka T, Matoba Y, Sawada K: Detection of specific IgE antibodies to nafamostat mesilate as an indication of possible adverse effects of leukocytapheresis using nafamostat mesilate as anticoagulant. *Ther Apher Dial* 8:45–51, 2004