Anaphylactoid Reaction Induced by Nafamostat Mesilate in a Hemodialysis Patient

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Dear Sir,

Nafamostat mesilate, 6-amidino-2-naph-thyl guanidinobenzoate dimethane sulfo-nate (Futhan®, Torii Pharmaceutical Co., Japan), is a serine protease-inhibiting agent discovered by Fujii and Hitomi [1]. It has been used since 1986, mainly for treating pancreatitis in Japan. Since Futhan has the preferable characteristics of a short-acting regional anticoagulant [2-4], it has also been used as an anticoagulant for hemodialysis patients with bleeding disorders for the past 6 years. Here we describe the first case of a Futhan-induced anaphylactoid reaction in a hemodialysis patient.

The patient was a 52-year-old woman with end-stage renal failure due to autosomal dominant polycystic kidney disease, who had been on hemodialysis using a polymethylmethacrylate membrane (Filtrizer BK-1.3P®, Toray Industries, Inc., Japan) 3 times/week since May 1991. She had no history of allergy. On September 16, 1994, she was treated for symptomatic hepatic cysts by means of percutaneous drainage. The next day, Futhan was used as an anticoagulant instead of heparin. She complained of nausea and vomiting for a few minutes upon initiation of hemodialysis. Dialysis was not interrupted. No treatment was necessitated. On October 6, 1994, she was admitted to our hospital due to obstruction of an internal shunt of expanded polytetrafluoroethylene used for hemodialysis. On October 20, 1994, she complained of nausea, vomiting, sweating, chest oppression and abdominal pain immediately after starting hemodialysis using Futhan. The blood pressure fell to 50 mm Hg by palpation. Hemodialysis was discontinued because of a suspected anaphylactoid reaction induced by Futhan. Fifteen hundred milligrams of hydrocortisone sodium succinate was infused. Her blood pressure was supported with an isotonic sodium chloride solution, norepinephrine and human serum albumin. Hemoconcentration developed acutely. Arrhythmia was not noted, nor were there any signs of myocardial ischemia on the electrocardiogram. Eosinophilia was not present. The above symptoms continued for 5 h and then gradually subsided. After the blood pressure had normalized, an extracorporeal ultrafiltration method was started with dalteparin sodium (Fragmin®, Kissei Pharmaceutical Co., Japan). No further episodes of anaphylactoid reaction were noted even though the patient

was switched to Fragmin and remained asymptomatic. Medications at the time of the episode were amezinium methylsulfate, precipitated calcium carbonate, gefarnate, cisapride, brotizolam and flunitrazepam. No antihypertensive, such as ACE-I, was administered. Although a direct ELISA for IgE against Futhan was negative, the drug lymphocyte stimulation test was positive for Futhan.

Based on these findings, a diagnosis of Futhan-induced anaphylactoid reaction was made. Several other known causes of an anaphylactoid reaction during hemodialysis can be excluded due to its disappearance after interruption of Futhan without any further change in treatment. The hypotensive episode in our patient more closely resembled an anaphylactoid reaction than endotoxic shock because it occurred early in the treatment and was not associated with fever. In this case, the anaphylactoid reaction developed at the beginning of the second use of Futhan. Although the exact mechanism of the reaction is not clear, Futhan seems to be the most likely precipitant of the anaphylactoid reaction in this patient.

Futhan is a strong protease inhibitor (100 times stronger than other antiproteases) with a molecular weight of 540 and its inhibitory action affects various enzyme systems including the coagulation and fibrinolytic systems (thrombin, the active forms of factors XII and X, plasma kallikrein, plasmin), kallikrein-kinin system (plasma kallikrein), complement system (C1r, C1s, B, D), pancreatic proteases (trypsin, pancreatic kallikrein) and phospholipase A₂. Thanks to its wide spectrum as a protease-inhibiting agent, Futhan is effective in treating pancreatitis, disseminated intravascular coagulation and shock.

The biological half-life of Futhan is less than 8 min and approximately 40% of the drug is dialyzed in the dialyzer [4]. Its anticoagulant effect is mostly limited to the extra-corporeal circulation. Akizawa et al. [2] reported three beneficial features of Futhan over heparin. Firstly, it does not affect the systemic coagulation. Secondly, it has a complement-inhibiting effect. Thirdly, it has no lipolytic activity. Accordingly, Futhan is also used as an anticoagulant for extracorporeal circulation in patients with hemorrhagic disease or bleeding tendencies in Japan.

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Adverse effects due to Futhan in hemodialysis patients have been reported. Akizawa et al. [2] described anorexia, general lassitude, slight myalgia and arthralgia, and Na-kanishi et al. [5] reported eosinophilia. These symptoms were eliminated after cessation of Futhan. The anaphylactoid reaction induced by Futhan in this patient has, as far as we are aware, not been reported previously.

In summary, this report describes the first case of an anaphylactoid reaction induced by Futhan as an anticoagulant in a hemodialysis patient. Although Futhan is thought to be an ideal anticoagulant in Japan, we should always be mindful of the possibility of an anaphylactoid reaction.

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