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Adverse Reactions to Protamine Sulfate used for Heparin Neutralization in a Dog Receiving a Blood Transfusion

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Abstract : A 14-year-old castrated male ShihTzu diagnosed with chronic kidney disease (CKD) 6 months prior was referred to our clinic. The patient had been experiencing symptoms such as vomiting, poor appetite and hind limbs weakness. Hematology tests showed that he had a non-regenerative anemia. With aggressive treatment, the patient's state had gotten worse. He showed ragged breath, vomiting blood and loss of consciousness temporarily. Hematocrit maintained low level. Gastric hemorrhage was strongly suspected by hematemesis. Whole blood transfusion was performed and heparin was used as an anticoagulant. Prior to transfusion, the blood cross matching between donor and patient was performed and the result was compatible. After the transfusion was stabilized, 1 mg of protamine sulfate for each 100 units of heparin was prepared and given intravenously over 3 minutes to reverse the effects of heparin. Immediately after protamine injection, the patient conducted severe anaphylactic shock. Protamine sulfate is used to reverse the anticoagulant action of heparin in dogs and humans. The adverse reaction of protamine sulfate range from mild reaction to fetal cardiac arrest. When using protamine sulfate as heparin neutralization, it can lead to the death of a patient cause of anaphylactic shock. For this reason, the protamine sulfate should be injected slowly with antihistamine and the clinician should carefully monitor patients.

Key words **:** dog, protamine sulfate, anaphylactic shock, heparin.

Introduction

Protamine sulfate is administered for the neutralization of heparin in both dogs and humans and has been known to cause variety of adverse reactions such as allergic reactions and systemic hypotension (2,9,14). Although the mechanisms of these adverse reactions by protamine sulfate have not yet been clarified, histamine mediated anaphylactic reaction is possible cause (14). This case report describes the application of protamine sulfate for heparin neutralization in a dog receiving a blood transfusion and an anaphylactic shock immediately after protamine injection.

Case

A 14-year-old castrated male ShihTzu with anorexia, depression and hind limb weakness was referred to Kyungpook National University Veterinary Medical Teaching Hospital. The patient had been diagnosed with chronic kidney disease (CKD) 6 months previously, but showed no clinical symptoms thereafter. The patient had been experiencing symptoms such as vomiting, poor appetite, and hind limb weakness for approximately 5 days. Thereafter, the owner took him to a local animal hospital where a complete blood count and serum biochemistry profile were performed. Hematology tests showed a decreased hematocrit (Hct) at 26.4% (reference index [RI]: 37-55%) and a slightly increased neutrophil count at 14.24×10^9/L (RI: 2-12 $\times 10^9$/L). Serum chemistry showed azotemia with blood urea nitrogen (BUN) levels at 130 mg/dL (RI: 7-2), creatinine at 7.3 mg/dL (RI: 0.5-1.8) and hyperphosphatemia (16.1 mg/dL; RI: 2.5-6.8 mg/dl). He was hospitalized and given intravenous fluids and routine treatments for CKD. However, the levels of BUN, creatinine and phosphorus increased steadily during hospitalization.

During the patient's first visit to our animal hospital, he was quiet but responsive, and had a pale mucous membrane. Thoracic auscultation revealed normal heart and lung sounds, with a heart rate of 150 beats per minute and a respiratory rate of 20 breaths per minute. Hematology, serum chemistry and routine urinalysis were performed. The hematology tests revealed anemia with Hct of 14.2% (RI: 36.9-55.0%), while serum chemical analysis showed elevated levels of BUN (173 mg/dL, RI: 9.2-29.2 mg/dL), creatinine (7 mg/dL, RI: 0.4-1.4 mg/dL) and phosphorous (20 mg/dL, RI: 1.9-5.0 mg/dL) levels. Urinalysis results were unremarkable aside from a urine specific gravity of 1.012.

The treatments initiated were aggressive fluid therapy with intravenous normal saline (7-10 mL/kg/h) and famotidine (0.5 mg/kg). Oral medications included metoclopramide (0.4 mg/kg), a routine gastric protective agent and adsorbents. Darbepoetin (0.3 μg/kg) was applied subcutaneously.

The following day, the patient's condition worsened. The owner reported that he was breathing raggedly, vomiting with

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hemorrhage and lost his consciousness temporarily overnight. Upon examination, the patient's mucous membrane was still pale, and he had been panting. Hct remained at 14.9, but gastric hemorrhage was suspected. In addition, the patient's mental and respiratory states worsened in comparison to the previous day; therefore, we decided to perform a blood transfusion. Prior to blood transfusion, blood cross matching between the donor and patient was performed and the result was compatible. We, then, prepared 150 mL of whole blood (with Hct of 54%) with heparin (500 IU per 50 mL of blood) as an anticoagulant. Pretreatment with dexamethasone (0.5 mg/kg) and diphenhydramine (1 mg/kg) was administered intravenously to help minimize adverse reactions. After transfusion, the state of the patient was stable. Since the patient had gastric hemorrhage, 1 mg of protamine sulfate per 100 units of heparin was prepared and administered intravenously over 3 minutes to reverse the effects of heparin. Within several seconds after protamine infusion, the patient showed open-mouthed breathing for a few seconds and loss of spontaneous breathing and pupillary light reflex. He then went into cardiac arrest. Cardiopulmonary resuscitation and intubation were performed immediately and epinephrine (0.02 mL/kg, three times, repeated every 2-3 minutes) was administered intravenously. Approximately 10 minutes later, the cardiac and respiratory efforts were restored but the patient did not regain consciousness. After 30 minutes, the patient showed a myoclonic status, and the owner decided to discontinue further treatments.

Discussion

Protamine sulfate is used to reverse the anticoagulant action of heparin in both dogs and humans. However, it can cause a variety of adverse reactions (2,9,14). Human studies have shown that 0.06-10.7% of people react to protamine sulfate, and the severity of the patients' reactions range from mild allergic reactions to fatal cardiac arrests (14). The major systemic reaction is hypotension, which can lead to cardiovascular collapse.

Studies on the usage and toxicity of protamine in dogs appear as early as 1900, but are fewer than in humans (1,3,6, 8,10,16-18). According to these studies, an injection of protamine in dogs changes the cardiovascular environment and pulmonary circulation. First, systemic blood pressure and systemic vascular resistance decreased after protamine administration (3,6,8,10,18). Jaques demonstrated a drop-in blood pressure to 30 mmHg that occurred 30 seconds after a protamine injection (10). In addition, protamine increases pulmonary artery pressure and pulmonary vascular resistance (3,8).

Although the exact mechanisms by which protamine sulfate produces these adverse reactions are unknown, anaphylactic and/or anaphylactoid reactions are possible causes (14). Both of these reactions are attenuated by the administration of histamine antagonists (13,14). Therefore, prophylactic administration of antihistamines is often used to reduce cardiovascular complications. Protamine and/or the protamine-heparin complex may elicit a release of histamine and stimulate vasodilation and hypotension (7). Histamine receptor blockers compete with histamine at receptor sites and attenuate any hemodynamic responses, although different studies have reported varying degrees of their efficacy (11,13).

To further reduce the risk of adverse reactions, it is important to inject protamine slowly (4,9,10,12,14). Several studies have shown that rapid injection increases protamine's cardiovascular effects. Thus, according to the current standard rate of slow infusion, protamine is administered over 5 to 15 minutes in humans (14).

While a slow rate of protamine infusion and antihistamine administration reduce some of the adverse reactions associated with protamine, they do not prevent all of them. These adverse reactions are usually dramatic and often life-threatening. In the present case, the veterinarian pretreated the patient with diphenhydramine and administered protamine cautiously, but the patient still went into an emergency state. A prolonged state of hypoperfusion, related to cardiopulmonary collapse, may lead to tissue ischemia, necrosis, and multiple organ failure. Therefore, when treating patients with protamine, their vital signs, hemodynamic parameters, respiratory function, and mental status should be carefully monitored.

There are currently no alternatives to protamine sulfate for neutralizing the anticoagulant effects of heparin. Toluidine blue and hexadimethrine bromide could be potential candidates, but both have significant side effects (5,15). In addition, not many sufficient animal studies have been performed regarding the use of these agents. Thus, protamine sulfate will continue to be used for reversing the anticoagulant activity of heparin after blood transfusion or cardiopulmonary surgery.

Some guidelines only describe that protamine should be slowly administered to dogs. However, dogs are more sensitive to protamine than humans; therefore, administration of protamine to dogs requires special attention (10,18). We recommend that an antihistamine should be administered to minimize any adverse reactions prior to using of protamine sulfate; thereafter, protamine sulfate should be injected very slowly. A safe administration method involves dividing the total dose of protamine in half and administering each half after an interval of 30-minutes. In addition, clinicians should carefully monitor the patient for the presence of any side effects.

References

1. Adkins JR, Hardy JD. Sodium heparin neutralization and the anticoagulant effects of protamine sulfate. Arch Surg 1967; 94: 175-177.
2. Carr J, Silverman N. The heparin-protamine interaction: a review. J Cardiovasc Surg 1999; 40: 659.
3. Chang L-C, Wrobleski S, Wakefield TW, Lee LM, Yang VC. Low molecular weight protamine as nontoxic heparin/low molecular weight heparin antidote (III): preliminary in vivo evaluation of efficacy and toxicity using a canine model. AAPS PharmSci 2001; 3: 24-31.
4. Ching KS, Leong DS. Cardiopulmonary effects of protamine in man. Anesthesiology 1980; 53: S116.
5. Eika C. On the mechanism of platelet aggregation induced by heparin, protamine and polybrene. Scand J Haematol 1972; 9: 248-257.
6. Fadali MA, Ledbetter M, Papacostas CA, Duke LJ, Lemole GM. Mechanism responsible for the cardiovascular depressant

effect of protamine sulfate. Ann Surg 1974; 180: 232-235.
7. Frater R, Oka Y, Hong Y, Tsubo T, Loubser P, Masone R. Protamine-induced circulatory changes. J Thorac Cardiovasc Surg 1984; 87: 687-692.
8. Goldman BS, Joison J, Austen WG. Cardiovascular effects of protamine sulfate. Ann Thora Surg 1969; 7: 459-471.
9. Horrow JC. Protamine: a review of its toxicity. Anesth Analg 1985; 64: 348-361.
10. Jaques LB. A study of the toxicity of the protamine, salmine. Br J Pharmacol Chemother 1949; 4: 135-144.
11. Kambam J, Meszaros R, Merrill W, Stewart J, Smith BE, Bender H. Prophylactic administration of histamine 1 and histamine 2 receptor blockers in the prevention of protamine-related haemodynamic effects. Can J Anesth 1990; 37: 420-422.
12. Li J, Hajarizadeh H, La Rosa C, Rohrer M, Vander Salm TJ, Cutler B. Heparin and protamine stimulate the production of nitric oxide. J Cardiovasc Surg (Torino) 1996; 37: 445-452.
13. Mayumi H, Toshima Y, Tokunaga K. Pretreatment with H2 blocker famotidine to ameliorate protamine-induced hypotension in open-heart surgery. J Cardiovasc Surg 1992; 33: 738-745.
14. Porsche R, Brenner ZR. Allergy to protamine sulfate. Heart Lung 1999; 28: 418-428.
15. Ransdell HT, Haller JA, Stowens D, Barton PB. Renal toxicity of polybrene (hexadimethrine bromide). J Surg Res 1965; 5: 195-199.
16. Wakefield T, Lindblad B, Whitehouse Jr W, Hantler C, Stanley J. Attenuation of hemodynamic and hematologic effects of heparin-protamine sulfate interaction after aortic reconstruction in a canine model. Surgery 1986; 100: 45-51.
17. Wakefield TW, Ucros I, Kresowik TF, Hinshaw DB, Stanley JC. Decreased oxygen consumption as a toxic manifestation of protamine sulfate reversal of heparin anticoagulation. J Vasc Surg 1989; 9: 772-777.
18. Yoo KY, Rim SJ, Shim SJ, Chung SS, Im WM. Mechanism of the Hypotension Produced Protamine Sulfate in Dogs. Korean J Anesthesiol 1998; 34: 27-38.