

Case Report

Allergic Shock and Death Associated With Protamine Administration in a Diabetic Patient

Yan-Qi Chu, MD¹; Li-Jian Cai, PharmD²; De-Chun Jiang, PharmD¹; Dan Jia, MD¹; Su-Ying Yan, MD¹; and Yu-Qin Wang, MD¹

¹Department of Pharmacy, Xuan Wu Hospital, Capital Medical University, Beijing, People's Republic of China; and ²Department of Pharmaceutical Services, University of Chicago Medical Center, Chicago, Illinois

ABSTRACT

Background: Insulin is used to treat patients with both type 1 and type 2 diabetes mellitus. Allergic reactions to insulin might be triggered by insulin itself or inactive ingredients in the insulin formulation, including proteins such as protamine in neutral protamine Hagedorn (NPH) insulin. The use of highly purified animal insulin and human recombinant insulin has reduced the incidence of anaphylactic reactions to insulin from ~30% to <1%.

Objective: We report a case of fatal allergic shock after the administration of protamine in a patient with a history of allergy to fish and a protamine-containing insulin.

Case summary: A 72-year-old Chinese male patient (height, 175 cm; weight, 80 kg) with a history of diabetes and progressive limb weakness was diagnosed with spinal vascular malformations after admission to the Xuan Wu Hospital of Capital Medical University, Beijing, People's Republic of China. He underwent epidural spinal cord arteriovenous fistula embolization with a liquid embolic agent (ethylene vinyl alcohol copolymer) after spinal cord angiography. During the operation, heparin was infused every hour with 6250, 2500, 2500, and 1250 IU, respectively. The last dose of heparin was administered ~10 minutes before the operation was completed. This was followed by the administration of protamine to neutralize the remaining heparin in the patient's body. Blurry vision and dizziness 5 minutes after protamine administration were followed by pruritus and hives over his neck and face. Oxygen was administered and 10 mg of dexamethasone with 2 mg of epinephrine was injected. The patient's heart rate dropped, his blood pressure decreased, and his arterial oxygen saturation (SaO₂) declined progressively. About 10 minutes after the administration of protamine

sulfate, the patient developed bradycardic arrest. Cardiopulmonary resuscitation efforts were undertaken and the patient was administered epinephrine 2 mg IV, atropine 0.5 mg IV, and subsequently, intravenous dopamine (50 mg/h). Ten minutes later, the patient's heart rate gradually increased, but blood pressure fluctuated, and SaO₂ ranged from 90% to 100%. Despite the initial response, the patient lost consciousness and heart rate declined progressively within 5 hours. Vasoactive agents including dopamine, norepinephrine, and adrenaline were administered. After all these measures proved ineffectual, the patient died. It was later determined that the patient had a history of allergic reactions to fish as well as to a premixed insulin that contained soluble human insulin 30% and low-protein intensive insulin zinc 70% (NPH). The Naranjo adverse drug reaction probability scale score for the association of protamine with the allergic reaction was 4, suggesting a possible relationship.

Conclusion: This case report highlights a preventable fatal allergic reaction possibly associated with protamine administration in a patient with a history of allergy to a protamine-containing insulin. (*Clin Ther.* 2010;32: 1729–1732) © 2010 Excerpta Medica Inc.

Key words: insulin allergy, protamine allergy, allergic shock, fatal.

INTRODUCTION

Insulin is used to treat both type 1 and type 2 diabetes mellitus. It has been reported that ~30% of diabetic

Accepted for publication August 10, 2010.

doi:10.1016/j.clinthera.2010.09.010

0149-2918/\$ - see front matter

© 2010 Excerpta Medica Inc. All rights reserved.

patients develop immunologic reactions to bovine and porcine insulin.^{1,2} Overall, allergic reactions to insulin have decreased to <1% since the introduction of highly purified recombinant human insulin.³ Allergic reactions have been reported in ~2% of patients receiving highly purified animal and human insulin therapy.² Some insulin preparations contain not only insulin, but also protamine sulfate and excipients such as glycerol, phenol, and dibasic sodium phosphate. Few allergic reactions to these other ingredients have been reported.⁴⁻⁶

Protamine is a polycationic peptide. Originally discovered in fish sperm, protamine sulfate is used to reverse heparin anticoagulation.⁷ Neutral protamine Hagedorn (NPH) insulin contains protamine to prolong the therapeutic effect of regular insulin and was commercially developed as a long-acting form of insulin treatment.⁸ NPH insulin is also associated with an increased risk for hypersensitivity to protamine in patients who have experienced an allergic reaction following a one-time exposure.⁹ Protamine sulfate has been reported to be associated with life-threatening anaphylactic reactions.¹⁰ Fish allergy has also been identified as one of the major risk factors for experiencing adverse effects from protamine.¹¹

We report a case of fatal allergic shock after the administration of protamine in a patient with a history of allergy to fish and a protamine-containing insulin.

CASE SUMMARY

A 72-year-old Chinese male patient (height, 175 cm; weight, 80 kg) with a history of diabetes and progressive limb weakness was diagnosed with spinal vascular malformations after admission to our hospital. He was admitted to the Xuan Wu Hospital, Capital Medical University, Beijing, People's Republic of China, on January 15, 2008. Iodine allergy test was negative. He underwent epidural spinal cord arteriovenous fistula embolization with a liquid embolic agent via transvenous catheter (Onyx-18, Micro Therapeutics Inc., Irvine, California) after spinal cord angiography.

Before the operation, 5 mL of 2% lidocaine solution was used for local anesthesia. At the beginning of the surgery, 250 mL of iohexol 300 mg/mL was infused through an arterial sheathing canal. No sedatives or muscle relaxants were used. During the operation, heparin was infused every hour with 6250, 2500, 2500, and 1250 IU, respectively. The last dose of heparin was administered ~10 minutes before the operation was completed. According to the $t_{1/2}$ of heparin, which is

~1 hour, when the surgery was ended, there would have been ~3000 IU of residual heparin in the patient's body. Protamine 1 mg can neutralize heparin 100 IU¹²; therefore, without any laboratory examination, 30 mg of protamine was infused to neutralize the heparin residues. The patient complained of blurry vision and dizziness 5 minutes after the protamine was administered. Subsequently, pruritus and hives developed over his neck and face. Oxygen was applied by a facemask and dexamethasone 10 mg with epinephrine 2 mg was injected. The patient's heart rate dropped to 50 beats/min, his blood pressure decreased from 140/75 to 120/50 mm Hg, and his arterial oxygen saturation (SaO_2) declined to 46.3% progressively. About 10 minutes after the administration of protamine sulfate, the patient developed bradycardic arrest. Cardiopulmonary resuscitation efforts were undertaken and the patient was administered epinephrine 2 mg IV, atropine 0.5 mg IV, and subsequently, intravenous dopamine (50 mg/h). Ten minutes later, the patient's heart rate gradually increased to 130 beats/min, blood pressure fluctuated between 130/60 and 70/30 mm Hg, and SaO_2 ranged from 90% to 100%. Despite the initial response, the patient lost consciousness and his heart rate declined again progressively within 5 hours. Vasoactive agents including dopamine, norepinephrine, and adrenaline were administered. These measures proved ineffectual and the patient died.

After the operation, a review of the patient's medical history revealed a fish allergy and a 21-year history of type 2 diabetes with no other disorders. The patient's family reported that he had started to use insulin to control blood glucose in the previous 5 years. He developed a generalized allergic shock reaction when he was administered premixed insulin (Novolin 30R, Novo Nordisk Pharmaceutical Industries, Inc., Bagsvaerd, Denmark). No allergic reactions were reported when he switched back to regular insulin.

A Naranjo adverse drug reaction probability scale score of 4 suggests the possibility of the allergic reaction being associated with protamine.¹³

DISCUSSION

The patient in our case had an allergic reaction to Novolin 30R, which contains protamine. The allergic reactions did not occur when the premixed insulin (Novolin 30R) was replaced with regular insulin. This suggests that protamine, and not insulin, may have been associated with the allergic reaction. This patient experienced

anaphylactic shock and died after the administration of protamine sulfate during surgery.

Allergic reactions caused by protamine have been reported for many years.¹⁴ The incidence of adverse events associated with protamine varies from 0.06% to 10.6%.¹⁵ Multiple cases have been reported that link fish allergy to an anaphylactic reaction to protamine.^{16–20} It has also been reported that patients with an allergy to NPH have a higher risk of developing an anaphylactic reaction to protamine.^{18,21–23} We conducted a search of published English-language literature in MEDLINE, ScienceDirect, and SpringerLink with no restriction on years, using the terms *allergy*, *anaphylactic reaction*, *protamine*, *insulin*, *excipients*, *insulin allergy*, *protamine allergy*, *allergic shock*, and *fatal*. To the best of our knowledge, the case we describe is the first to link fish allergy, NPH allergy, and a protamine anaphylactic reaction. The causal relationship between exposure and reaction is considered “possible” with the utilization of the Naranjo algorithm.¹³ To the best of our knowledge, this is also the first case report of an adult with a history of fish allergy and an adverse reaction to Novolin 30R, who subsequently developed anaphylactic shock due to protamine.

For this case, all of the necessary information was available to prevent this patient from receiving protamine and yet it still happened. The patient information was not shared among the different hospitals because this patient had seen doctors in hospitals that were in 2 different provinces. The patient’s history should have been determined each time. Second, the paper documentation could not be shared with the pharmacy through the Hospital Information System (HIS) in one hospital, because the HIS was only partially automated. The complaint, medical history, family history, and physical examination were recorded manually; only the medications used in-hospital were entered into the computer. Therefore, the pharmacists could not access the case history through the HIS. In addition, medical references, prescribing information, and decision-support systems should have been updated to include this information. For example, the package insert of protamine sulfate had no relative information regarding this possible adverse reaction.

Going forward, our pharmacy should send a card with adverse reaction information for physicians when they need to prescribe medication. In individual hospitals, electronic information systems should be accessible so that patient information can be available for every medical worker. In China, electronic medical record

systems need to be in widespread use. This might help to alert clinicians to the development of fatal anaphylactic shock with commonly used insulin preparations and protamine sulfate. When this adverse event occurred, it was reported to the National Center for Drug Re-evaluation of China.

Careful review of allergy history and critical evaluation of commonly used medicinal preparations, along with the utilization of decision-support systems, may prevent similar reactions to protamine-containing medications.

CONCLUSIONS

We report a case of a patient with a history of allergic reactions to fish and Novolin 30R, who was subsequently administered protamine sulfate following heparin administration and died because of an anaphylactic reaction. This case report highlights a preventable fatal allergic reaction possibly associated with protamine administration in a patient with a history of allergy to a protamine-containing insulin.

ACKNOWLEDGMENTS

All of the authors wish to thank Professor Ishaq Latin, PhD (Department of Pharmaceutical Services, University of Chicago Medical Center, Chicago, Illinois), for his help in revising the manuscript for clarity and grammar.

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Drs. Chu, Cai, Jiang, and Jia were involved in drafting the manuscript and were responsible for the patient’s medical assistance. Drs. Yan and Wang coordinated the discussion to determine the reason for this case report. All authors read and approved the final manuscript.

REFERENCES

1. Scherthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care*. 1993;16 (Suppl 3):155–165.
2. Fineberg SE, Huang J, Brunelle R, et al. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care*. 2003;26:89–96.
3. Heinzerling L, Raile K, Rochlitz H, et al. Insulin allergy: Clinical manifestations and management strategies. *Allergy*. 2008;63:148–155.
4. Rajpar SF, Foulds IS, Abdullah A, Maheshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. *Contact Dermatitis*. 2006;55:119–120.

5. Kim D, Baraniuk J. Delayed-type hypersensitivity reaction to the meta-cresol component of insulin. *Ann Allergy Asthma Immunol.* 2007;99:194-195.
6. Panos A, Orrit X, Chevalley C, Kalangos A. Dramatic post-cardiotomy outcome, due to severe anaphylactic reaction to protamine. *Eur J Cardiothorac Surg.* 2003;24:325-327.
7. Shenoy S, Harris RB, Sobel M. Development of heparin antagonists with focused biological activity. *Curr Pharm Des.* 1999;5:965-986.
8. Peterson GE. Intermediate and long-acting insulins: A review of NPH insulin, insulin glargine and insulin detemir. *Curr Med Res Opin.* 2006;22:2613-2619.
9. Lee AY, Chey WY, Choi J, Jeon JS. Insulin-induced drug eruptions and reliability of skin tests. *Acta Derm Venereol.* 2002;82:114-147.
10. Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: A systematic literature review. *Basic Clin Pharmacol Toxicol.* 2008;103:192-196.
11. Porsche R, Brenner ZR. Allergy to protamine sulfate. *Heart Lung.* 1999;28:418-428.
12. Sweetman, SC, ed. *Martindale: The Complete Drug Reference, 35th ed.* London, UK: Pharmaceutical Press; 2007.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245.
14. Pföhler C, Müller CS, Hasselmann DO, Tilgen W. Successful desensitization with human insulin in a patient with an insulin allergy and hypersensitivity to protamine: A case report. *J Med Case Reports.* 2008;2:283.
15. Weiler JM, Gelhaus MA, Carter JG, et al. A prospective study of the risk of an immediate adverse reaction to protamine sulfate during cardiopulmonary bypass surgery. *J Allergy Clin Immunol.* 1990;85:713-719.
16. Knappe JT, Schuller JL, de Haan P, et al. An anaphylactic reaction to protamine in a patient allergic to fish. *Anesthesiology.* 1981;55:324-325.
17. Caplan SN, Berkman EM. Letter: Protamine sulfate and fish allergy. *N Engl J Med.* 1976;295:172.
18. Levy JH, Schwieger IM, Zaidan JR, et al. Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg.* 1989;98:200-204.
19. O'Neil C, Helbling AA, Lehrer SB. Allergic reactions to fish. *Clin Rev Allergy.* 1993;11:183-200.
20. Mukadam ME, Pritchard P, Ridlington D, et al. Management during cardiopulmonary bypass of patients with presumed fish allergy. *J Cardiothorac Vasc Anesth.* 2001;15:512-519.
21. Gottschlich GM, Gravlee GP, Georgitis JW. Adverse reactions to protamine sulfate during cardiac surgery in diabetic and non-diabetic patients. *Ann Allergy.* 1988;61:277-281.
22. Levy JH, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. *Anesth Analg.* 1986;65:739-742.
23. Stewart WJ, McSweeney SM, Kellett MA, et al. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation.* 1984;70:788-792.

Address correspondence to: Yu-Qin Wang, MD, Department of Pharmacy, Xuan Wu Hospital, Capital Medical University, Beijing, People's Republic of China. E-mail: yuqwang@sina.com