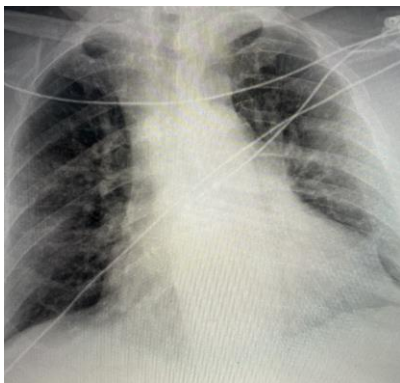


Introduction

- Protamine is used to reverse the anticoagulant effects of heparin, commonly seen in the setting of an operating room. As with administration of any medication, protamine comes with risks; adverse effects include an anaphylactic response, impact on platelet function, pulmonary hypertension, and hypotension.
- Historically, patients with allergies to fish were known to develop severe reactions to protamine sulfate as there is a high concentration of protamine in certain parts of fish. Therefore, protamine as a reversal agent was avoided in these groups of people. Later, it was noted that there was an increased incidence of severe reactions in certain diabetics. It was discovered that those on NPH insulin had an increased risk of developing these adverse reactions.
- Protamine is present within the formulation of NPH insulin, leading to the development of antibodies to protamine within these patients over time. Although these reactions have been well documented, a comprehensive home medication review prior to the administration of protamine is not routinely performed. This leads to an increased chance of a diabetic patient on NPH insulin at home to develop a severe reaction



Radiograph of increasing pulmonary vascular congestion after protamine

Case Description

- Here we examine a 75-year-old male with past medical history of hypertension, type 2 diabetes, hyperlipidemia, and obstructive sleep apnea who presented to the emergency department for a diabetic ulcer on the lateral aspect of his right ankle.
- Prior to his arrival, the patient was on Humalog 70/30 twice daily, 78 units in the morning and 70 units at night. He was also on Metformin. Both of these medications were continued throughout his hospital stay with sliding scale insulin parameters in place as well. He was initiated on heparin for deep venous thrombosis prophylaxis.
- Imaging findings were concerning for osteomyelitis and arterial studies showed multilevel arterial disease. The patient was scheduled for an angiogram with endovascular intervention the next day which would be followed by debridement the following day.
- He was taken to the operating room and underwent successful balloon angioplasty of distal superficial femoral artery and posterior tibial artery.
- The patient was receiving protamine sulfate for reversal of heparin during this time, and it was reported that he developed a sudden reaction. He had received only 10 mg of the protamine infusion before there was a rapid onset of a flushed appearance. He stopped breathing for a few seconds and second-degree heart block was observed on cardiac monitoring.
- The protamine infusion was immediately discontinued. There was a resolution of symptoms within two minutes of discontinuing the infusion. The patient was placed on nonrebreather given hypoxia and residual shortness of breath and he was transferred to the ICU for closer monitoring.
- A chest x ray was obtained following this reaction and showed mild pulmonary vascular congestion leading to the initiation of Bumex. The next day, the patient demonstrated improvement and his oxygen requirements decreased to two liters nasal cannula.
- Additionally, improvement in bilateral lower extremity edema was noted. Both cardiology and pulmonology were consulted for further evaluation and deemed him medically stable for his debridement procedure with recommendations to avoid protamine sulfate use in the future.

Discussion

- Protamine sulfate has a long standing history of being used as a procoagulant and it has been in use since 1939.
- The use of protamine in patients with fish allergies can lead to an anaphylactic response.
- Patients with use of NPH insulin that receive protamine sulfate have less recorded severe reactions in comparison to those with fish allergies.
- However, there have been multiple recorded cases of fatal reactions in these patients requiring the use of catecholamines.
- In fact, there is a 50-fold increased risk for severe reaction in patients that use NPH insulin compared to those using other formulations of insulin.
- It is preferred that both patients with allergies to fish and use of NPH insulin do not have protamine used intraoperatively.

Conclusion

- A thorough history review should be performed before the administration of protamine, including home medications, allergies, past surgical history.
- Comprehensive history can prevent further occurrences of potentially fatal protamine reactions.

References

- Stewart, W. D. P., McSweeney, S., Kellett, M., Faxon, D. P., & Ryan, T. J. (1984d). Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation*, 70(5), 788–792. <https://doi.org/10.1161/01.cir.70.5.788>