Alternatives to protamine for reversal of unfractionated heparin (UFH) during a shortage

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INTRODUCTION

Unfractionated heparin (UFH)[1,2]

- Anticoagulant for venous thromboembolic disorders or complications and prevention of clotting associated with atrial fibrillation or cardiac surgery
- Mechanism: Inactivates thrombin and prevents conversion of fibrinogen to fibrin
- Warning(s): Increased risk of bleeding in patients over the age of 60
    - Higher incidence in women
    - Bleeding is the chief sign of overdose such as nosebleeds
- Limitation: Protamine is the only FDA approved reversal agent

Protamine[1,2]

- FDA approved unfractionated heparin reversal agent
- Mechanism: forms a stable salt which nullifies anticoagulant activity.
- Warning(s): High doses turn protamine into an anticoagulant
    - Heparin rebound associated with anticoagulation and bleeding can occur
    - Symptoms typically occur about 8-9 hours after administration, but can occur up to 18 hours later
- **Anticipated shortage due to increased demand [3]**

OBJECTIVE

This literature review evaluates available alternatives for protamine when the use of unfractionated heparin is unavoidable.

METHODS

A literature search was conducted in July 2019.

- Databases searched: MEDLINE, Embase, International Pharmaceutical Abstracts, and Clinicialtrials.gov
- Search terms: “heparin,” “antidote,” “protamine,” “cardiopulmonary bypass,” “reversal,” “unfractionated heparin,” “alternative”
- Studies evaluating possible alternatives for the reversal of protamine were included in this review.

RESULTS

Table 1. Reversal agents under investigation in preclinical development phase.

Agent	Targeted Anticoagulants	Mechanism of Action	Dosing	Elimination Half-life
Heparinase[4]	UFH	Neutralizes heparin by enzymatic cleavage of alpha glycosidic linkages at the antithrombin III (AT III) binding site	300 units/kg	18 min
Universal Heparin Reversal Agent (UHRA)[5]	UFH, LMWH, fondapinux	Dendritic polymer scaffold that binds UFH, LMWH, and fondaparinux through trivalent cationic groups based on charge and interactions	50 mg/kg	40 min
Recombinant inactive antithrombin (riAT)[6]	UFH	Dose dependent antifactor Xa and antifactor IIa	37.5 mg/kg	--
Dex40-GTMAC3[7]	UFH	Binds UFH through charge interactions as a high weight molecular dextran with GTMAC groups	7.5 mg/100 UI IV	12 min
Histidine-rich glycoprotein (HRG) plus zinc [8]	UFH	Binds to UFH by using a variety of ligands, proteins (plasminogen, fibrinogen, thrombospondin), heparin and transition metals coordinated by imidazole side chains where heparin binding occurs and is enhanced by electropositive histidine	Dosing under investigation due to toxic levels	--
Quarternized chitosan derivative[9]	UFH, LMWH	Forms a stable complex with UFH and LWMH through positive charges of its chain which completely bind to free UFH and LWMH	1 mg/kg (100 U/kg) of UFH	--
LMWP[10]	UFH	Combination of 2 arginine clusters (each made up of 4 to 6 arginine residues) in a peptide with full heparin affinity	2.2 mg/ 100 IU of UFH	--

- Based on available literature the following compounds have been investigated as alternatives: hexadimethrine bromide, heparinase, platelet factor 4 (PF4), heparin removal devices, synthetic protamine variants, methylene blue, vancomycin, tolonium chloride, ciraparantag, universal heparin reversal agent (UHRA), Dex40-GTMAC3, histidine-rich glycoprotein (HRG) plus zinc, recombinant inactive antithrombin (riAT), low molecular weight protamine (LMWP) and quaternized chitosan derivative.
- Alternatives to the heparin/protamine combination were also investigated.
    - Bivalirudin works as a specific and reversible direct thrombin inhibitor with an indication for percutaneous coronary intervention (PCI) and heparin-induced thrombocytopenia/thrombosis syndrome (HIT/TS).[10]
        - Bivalirudin is currently available as an alternative for cardiopulmonary bypass surgery and eliminates the use of an antidote due to the short half-life of 25 minutes.[11]
    - The pegnivacogin/anivamersen combination along with FIXa aptamer antidote pair are promising alternatives currently in the pipeline for patients with acute coronary syndromes and those undergoing PCI.[12]

Abbreviations: HIT, heparin-induced thrombocytopenia; TS, thrombosis syndrome; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; LMWH, low molecular weight heparin; LMWP, low molecular weight protamine

CONCLUSION

Protamine remains as the only FDA approved reversal agent for unfractionated heparin. Unfortunately, there are no alternatives readily available for use in the event of protamine shortage.

- Due to lack of protamine alternatives, substitutions for the heparin/protamine combination such as bivalirudin should be considered in appropriate procedures.

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DISCLOSURES

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

John Maneno, PharmD; Andrew Douglas, PharmD, MPH; Genevieve Lynn Ness, PharmD: Nothing to disclose.