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

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INTRODUCTION

Unfractionated heparin (UFH)1,2,3
• Anticoagulant for venous thromboembolic disorders or complications
• Prevention of clotting associated with atraumatic 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

Binds to UFH by using a variety of ligands, proteins (plasminogen, fibrinogen, factor VIII, thrombomodulin), and cellular components.

Universal Heparin Reversal Agent (UHRA)4
• UFH, LMWH, fondaparinux
• Dendritic polymer scaffold that binds UFH, LMWH, and fondaparinux through divalent cationic groups based on charge and interactions

Recombinant inactive antithrombin (riAT)5
• Dose dependent antifactor Xa and antifactor IIa

Bivalirudin is currently available as an alternative for cardiopulmonary bypass surgery and eliminates the use of an antidote

Mechanism: Inactivates thrombin and prevents conversion of fibrinogen to fibrin

Heparin

Protamine is the only FDA approved reversal agent

FDA approved unfractionated heparin reversal agent
• Mechanism: Forms a stable salt which nullifies anticoagulant activity.
• Warning(s): High dose turns protamine into an anticoagulant
• 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

OBJECTIVE

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

METHODS

A literature search was conducted in July 2019.
• Databases searched: MEDLINE, Embase, International Pharmaceutical Abstracts, and Clinicaltrials.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. Reversible agents under investigation in preclinical development phase.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Targeted Anticoagulants</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Elimination Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirudin</td>
<td>UFH</td>
<td>Neutralizes by enzymatic cleavage of alpha glycosidic linkages at the antithrombin III (AT III) binding site</td>
<td>800 units IV</td>
<td>18 min</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>UFH</td>
<td>Binds to UFH by using a variety of ligands, proteins (plasminogen, fibrinogen, thrombomodulin), and cellular components.</td>
<td>50 mg/kg</td>
<td>40 min</td>
</tr>
<tr>
<td>Dose dependent antifactor Xa and antifactor IIa</td>
<td>UHRA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>37.5 mg/kg</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>Binds UFH through charge interactions as a high weight molecular dextran with GATMAC groups</td>
<td>7.5 mg/100 UI IV</td>
<td>12 min</td>
<td></td>
</tr>
<tr>
<td>Heparin-targeted glycoprotein (HRG) plus zinc</td>
<td>UFH</td>
<td>Binds to UFH by using a variety of ligands, proteins (plasminogen, fibrinogen, thrombomodulin), and cellular components.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/kg (100 U/kg) of UFH</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forms a stable complex with UFH and LMWH with positive charges of its chain which completely bind to free UFH and LMWH</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.2 mg/100 U of UFH</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWP</td>
<td>Combination of 2 arginine clusters (each made up of 4 to 6 arginine residues) in a peptide with full heparin affinity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.5 mg/kg</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Based on available literature the following compounds have been investigated as alternatives: hexadimethrine bromide, heparin, platelet factor 4 (PF4), heparin removal devices, synthetic protamine variants, methylene blue, vancomycin, toluyloxym chloride, ciraparantag, universal heparin reversal agent (UHRA), Dext40-GATMAC, 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).6
  • 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.7
  • The pegivacogin/aniexamersen combination along with FXa apater antidote partner are promising alternatives currently in the pipeline for patients with acute coronary syndromes and those undergoing PCI.8

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.

REFERENCES

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DISCLAIMERS

Authors of this presentation have the following 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

No disclosures.

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