HEPARIN RESISTANCE

Maanas Deodhar1, Srishti Sawant1, Surabhi Fadnavis1,
Atul Laddu1, Fakiha Siddiqui2, Jawed Fareed2, and Parth Rali3
1Global Thrombosis Forum, Suwanee, GA
2Loyola University, Chicago, IL
3Lewis Katz School of Medicine, Philadelphia, PA

BACKGROUND

Heparin (Figure 1) is a negatively charged, sulfated glycosaminoglycan polysaccharide polymer isolated from the porcine intestine, and stored in mast-cell granules.
Unfractionated heparin (UFH) is a mixture of polymers with chain lengths ranging from 3000 to 30,000 daltons ($\bar{x}$ = 15,000). Low-molecular-weight heparin (LMWH), purified from UFH, has a more uniform polymer size and a molecular weight of 3500 to 5000 daltons. Although UFH has greater interindividual variation in pharmacodynamic effects than LMWH heparin, its short half-life and rapid reversibility with the administration of protamine make it the anticoagulant of choice when careful control of anticoagulation is needed.
We reviewed the literature and have summarized the results of our research.

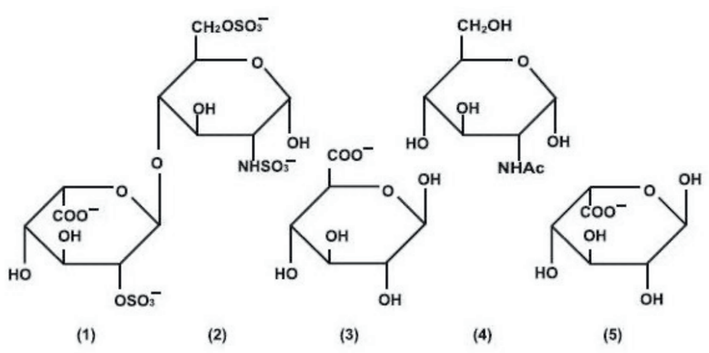

Figure 1: Chemical structure of Heparin

METHODS

Heparin resistance (HR)

- Drug resistance describes a reduced response to a given dose of a therapeutic agent, which can preexist or be triggered by prior drug exposure.
- There are multiple causes of drug resistance, including inadequate dosing and/or potential adaptive change in the medication's target that occurs in antibiotic or chemotherapeutic drug resistance.
- HR is often defined as the need for high heparin doses to achieve a targeted level of anticoagulation, yet the threshold dose is not well defined.

RESULTS

History of HR

- Hagedorn and Barker reported "hypo-responders" to heparin more than 75 years ago.
- The dose-response curve to UFH based on whole blood clotting tests was altered in some individuals.
- American College of Chest Physicians defined HR in nonsurgical patients as a "situation wherein patients require unusually high doses of heparin to achieve a therapeutic aPTT.
- Heparin resistance, or responsiveness issues, can occur in heparin-requiring surgeries, and administering additional heparin to overcome resistance could lead to bleeding at the end of the procedure

Incidence of HR

Heparin resistance occurs in up to 22% of patients undergoing cardiac surgery requiring cardiopulmonary bypass and it is associated with decreased levels of ATIII.

What causes HR?

- Antithrombin III (ATIII) deficiency is the most common cause of low heparin response
- Congenital deficiencies of ATIII
- Use of high doses of heparin
- HR becomes a concern when greater than 35,000 IU/day is required to get a subtherapeutic or negligible response.
- The most cost-effective and widely used tests to check for therapeutic levels of ATIII are aPTT and ACT.

Predictors of HR

- ATIII Activity less than or equal to 60%
- Platelets greater than 300,000
- Age 65 and above
- Increased Factor VIII and fibrinogen levels

Location of Anticoagulant Targets in Coagulation Pathways (Figure 2)

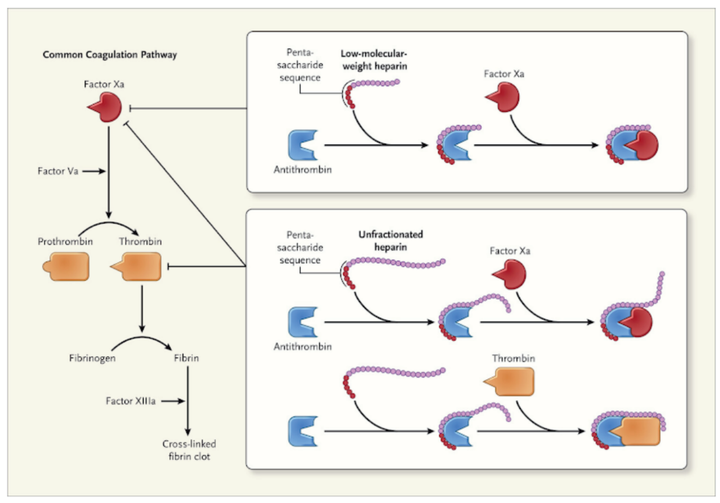

Figure 2. Location of Anticoagulant Targets in Coagulation Pathways.

The Role of ATII in Thrombosis

- 80% of the natural anticoagulant effect against thrombin is dependent on ATIII
- ATIII activity inhibits many clotting factors in the coagulation cascade

Cofactor Relationship Between ATIII and Heparin

- ATIII inactivates multiple clotting factors in the coagulation cascade
  - Binds irreversibly/inhibits prothrombotic actions of factor Xa and thrombin
- The anticoagulant effects of heparin rely on its interaction with ATIII
  Heparin depends on ATIII as a cofactor
- Heparin is ineffective in the absence or near absence of ATIV.
- The anticoagulant activity of ATIII is accelerated >1000X when bound to administered heparin

Types of ATIII deficiencies

Congenital ATIII deficiencies

Reduced levels of ATIII
- Reduced synthesis and or stability secondary to the gene mutations
- Mutations leading to reduced activity.

Acquired ATIII deficiencies

- Disseminated intravascular coagulation (DIC)
- Acute thrombosis
- Liver cirrhosis
- Nephrotic syndrome
- Hemodialysis

Management of HR

1. Administration of ATIIII

2. Administration of fresh frozen plasma

3. Anti–factor Xa to measure the heparin level. If the anti-factor Xa level is low, then the dose of UFH should be increased to achieve the standard target of 0.3 to 0.7 IU per milliliter.

4. Direct Thrombin Inhibitors (argatroban and bivalirudin) are administered intravenously primarily in patients with heparin-induced thrombocytopenia. These agents directly inhibit thrombin without requiring antithrombin and are frequently administered in critically ill patients, including those with COVID-19.

CONCLUSIONS

Heparin is a negatively charged, sulfated glycosaminoglycan polysaccharide polymer isolated from the porcine intestine, and stored in mast-cell granules. HR is induced due to high-dose administration of UFH. The incidence of HR is 22%. In a patient having HR, the physician can unintentionally deliver large amounts of UFH to produce therapeutic effects, causing heparin toxicity. HR is diagnosed when ATIII activity is less than or equal to 60%, platelets greater than 300,000, or increased Factor VIII and fibrinogen levels. The management of HR can be through the administration of ATIII or the administration of fresh frozen plasma.