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A Brief Review on Heparine

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ABSTRACT: Heparine has been used the extensively as an antithrombotic and anticoagulant for close to 100 years. This is anticoagulant activity is attributed mainly to the pentasaccharide sequence, which potentiates the inhibitory action of antithrombin, a major inhibitor of the coagulation cascade. More recently it has been elucidated that heparin exhibits anti-inflammatory effect via interference of the formation of neutrophil extracellular traps and this may also contribute to heparin's antithrombotic activity. This illustrates that heparin interacts with a broad range of biomolecules, exerting both anticoagulant and nonanticoagulant actions. Since our previous review, there has been an increased interest in these nonanticoagulant effects of heparin, with the beneficial role in patients infected with SARS2-coronavirus a highly topical example. This article provides an update on our previous review with more recent developments and observations made for these novel uses of heparin and an overview of the development status of heparin-based drugs.

KEYWORDS: heparin, heparan sulfate, heparin-like molecules, bioengineering, UFH, low molecular weight heparin, anti-inflammatory, antitumor, Chinese hamster ovary cells

INTRODUCTION:

The recent thrombotic events related to COVID-19 infection and vaccination have highlighted the efficacy of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) not only as antithrombotic/anticoagulants but potentially for the anti-inflammatory and antiviral properties of these drugs (van Haren et al., 2020). The history of the discovery of heparin and its subsequent use as an anticoagulant are covered by several detailed reviews (Barrowcliffe, 2012; Hemker, 2016). Briefly, heparin as an anticoagulant was first described by Maurice Doyon in 1910 (Doyon et al., 1911). However, the discovery of heparin has been ascribed to Jay Mclean, who copurified an anticoagulant substance while extracting procoagulant thromboplastin fractions from different tissue sources (McLean, 1916). While UFH was first used as a clinical product in the 1930s, developed by Charles Best in Canada and Erik Jorpes in Sweden, the critical antithrombin binding pentasaccharide sequence and its mechanism of action were not elucidated until the 1970s (Lindahl et al., 1979; Rosenberg and Lam, 1979; Choay et al., 1980). The 1970s also heralded the discovery of LMWH (Johnson et al., 1976). Figure 1 illustrates the important chronological milestones in the development and use of heparin and LMWH.

MECHANISM OF ACTION:

Once administered, heparin binds to several proteins; however, it is binding to an antithrombin that is important, as this causes a surface change and inactivates thrombin. Binding to antithrombin blocks several different factors of the clotting cascade, but two are predominant: thrombin (Factor IIa) and Factor Xa. By inactivating thrombin, it blocks the conversion of fibrinogen to fibrin; this prevents the formation of clots and prolongs the clotting time of blood. Heparin does not affect bleeding time, but it does prolong the time that blood takes toclot.

ANALYSIS OF HEPARINE:

A.Analytical methods of pharmaceutical heparine:

Disaccharide compositional analysis for quality control of pharmaceutical heparin can be achieved by either 2D NMR (Mauri et al., 2017a) or chromatographic separation of disaccharides from exhaustive digestion with heparinases, detected by fluorescence and mass spectrometry (Galeotti and Volpi, 2016). NMR-based and chromatographic approaches have been compared

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(Spelta et al., 2019), and a combination of these approaches was found to provide accurate differentiation of species and organ sources of heparin.
The anticoagulant methods used to determine heparine activity are described in section 5.9 .

B.Responce to contamined heparine :

Since the episode of contamination of pharmaceutical heparin with OSCS in 2007–2008 that led to serious adverse events associated with the clinical use of certain heparin preparations, including fatalities (Chess et al., 2012), development of new methods for the assessment of heparin continues (Devlin et al., 2019). It has now been established that the contaminant OSCS was added at an early stage of heparin manufacture, so methods applicable to the efficient screening of crude heparin samples rather than API and final product are particularly useful (Mauri et al., 2017b; Mendes et al., 2019) in ensuring such contamination does not occur in the future.

C.INTRODUCTION OF HEPAEINE FROM OTHER SPECIES:

Structural and functional differences between heparin from different sources have implications for regulatory matters. For example, the Brazilian Pharmacopeia has separate monographs for bovine and porcine heparin from intestinal mucosa, with different acceptance criteria for the two heparin types (Vilanova et al., 2019b). Methods for distinguishing between BLH, BMH, OMH, and PMH are discussed in Section 2.9. Surveys of recently manufactured BMH have shown that overall levels of impurities (whether protein, nucleic acid, or galactosamine containing GAGs) in BMH are comparable to those observed in PMH (Workman and Carrick, 2020); molecular weight distributions for the same set of BMH samples vary more than do current PMH samples (Bertini et al., 2017c).

ADMINISTRATION:

Heparin administration can be by intravenous (IV) route or subcutaneous SQ) route. Intravenous heparin is continuously administered for therapeutic anticoagulation, while intermittent subcutaneous administration is used to prevent thromboembolism. Intermittent IV administration is also an option. For example, heparin is given intermittently by the interventional cardiologist in the cardiac catheterization lab, dependent upon laboratory markers throughout the case. When administered SQ, the onset of action is usually within 1 to 2 hours compared to an immediate anticoagulant effect with IV administration of heparin. There was an assessment of intramuscular (IM) injection, but researchers observed an increased level of pain, irritation, and hematoma formation with IM injections of heparin.

ADVERSE EFFECTS:

Heparin use's typical adverse effects include bleeding, thrombocytopenia, injection site reactions, and other adverse effects only seen with chronic heparin administration. Bleeding is a major complication associated with heparin use. Patients should undergo monitoring for new bleeding that may present in the urine or stool. Bleeding may also present as bruising, petechial rash, and nosebleeds.

Thrombocytopenia typically occurs in up to 30% of patients who receive heparin. Most often, this is not significant; however, there is a form of thrombocytopenia that is more serious, known as heparin-induced thrombocytopenia (HIT). Thrombocytopenia can be classified as Type I or Type II. Type I is a non-immunogenic interaction with platelets that typically occurs within the first 48 to 72 hours of initiation of heparin. The drop in platelet count is usually temporary and will recover upon cessation of heparin. Type II thrombocytopenia is more commonly known as heparin-induced thrombocytopenia; this is immune-related thrombocytopenia that occurs when heparin binds to the protein platelet factor 4 (PF4).Thrombosis can form and cause severe HITT (heparin-induced thrombocytopenia and thrombosis). Serious events seen with thrombosis include pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, and thrombosis in main arteries to organs that could lead to severe complications, including limb amputation or death.
Other adverse effects that occur with the use of heparin include injection site reactions, hyperkalemia, alopecia, and osteoporosis. Osteopenia and osteoporosis have correlations with chronic heparin use, but not with acute use of heparin.

CONTRAINDICATIONS:

A patient should not receive heparin

- The platelet count is 100,000/mm or lower.
- The patient cannot have routine monitoring tests performed to monitor therapeutic heparin.
- The patient has an active, uncontrollable bleed except for disseminated intravascular coagulation (DIC).

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- Patients with a history of heparin-induced thrombocytopenia should also avoid heparin use.

MONITORING:

Therapeutic monitoring for heparin includes activated partial thromboplastin time (aPTT) and activated clotting time (ACT). Both of these are aspects of clotting time, which are prolonged by therapeutic heparin doses. Activated partial thromboplastin time is performed at baseline and every 6 hours until 2 or more therapeutic values are obtained, then aPTT can be assessed every 24 hours. Dose titrations are made based on the results of the aPTT. Hospitals have dosing nomograms specific to their target aPTT, which may vary depending upon the laboratory reagent used for their test. Therapeutic aPTT is considered therapeutic at 1.5 to 2 times control, which also varies from facility to facility based on controls.

Monitoring for adverse effects includes hemoglobin, hematocrit, platelet count (every 2 to 3 days while on therapy), and vital signs. If hemoglobin, hematocrit, or blood pressures drop, the possibility of hemorrhage should be investigated. If the platelet count falls below 100000/mm3, then the risk and benefit of continuing heparin should be evaluated, and an alternative anticoagulant is the recommended course. A HIT 4-T score should be calculated when HIT is suspected.

TOXICITY:

When heparin toxicity occurs, protamine is recommended for reversal of heparin's anticoagulant effect. Patients with life-threatening or severe bleeding or patients who undergo surgery may require protamine for reversal. Neutralization of heparin occurs when protamine binds to the heparin by ionic properties. The protamine-heparin complex is inactive, and heparin is unable to act as an anticoagulant. Protamine administration should be via slow IV push with no more than 50 mg over 10 minutes. Administration of protamine too rapidly has been associated with severe reactions, most commonly, hypotension, pulmonary edema, pulmonary vasoconstriction, and pulmonary hypertension. These effects also present with high doses of protamine, repeat doses of protamine, and previous exposure or current exposure. Anaphylaxis can also occur with protamine administration. Because of heparin's short half-life, time from administration of heparin is used to determine the initial dose of protamine needed for reversal. Every 1mg of protamine administered neutralizes 100 units of heparin. Heparin neutralization should occur within about 5 minutes of protamine administration.

ENHANCING HEALTHCARE TEAM OUTCOMES:

Heparin enjoys wide use in the hospital setting for several different indications that require specific dosing and administration routes. The use of heparin is a balance between effective anticoagulation to treat or prevent thromboembolism and safety. According to ISMP (Institute for Safe Medication Practices), heparin is in the high-risk medication classification that correlates with a multitude of patient safety errors and has the potential to cause significant harm. Many factors can contribute to potential errors, including dosing, monitoring, adverse effects, and dispensing logistics. To mitigate these potential errors, major safety monitoring organizations and several clinical studies have been conducted to delineate the most effective management standards for hospitals. Collectively, more information available about past errors can influence practice to protect patients.There are numerous documented heparin errors attributed to manufacturer labeling and the many stock vials and bags available. After fatal errors in the pediatric population, a labeling update was instituted in 2013 to display the total number of units in each heparin vial. Limiting current stock to a standard heparin bag solution and standard vial concentrations for automatic dispensing cabinets may also help to prevent errors.

In conclusion, heparin is a high-risk medication that requires many safety barriers to avoid errors and protect patients; this takes an interprofessional team approach in the hospitals consisting of clinicians (MDs, DOs, NPs, PAs), nurses, and pharmacists. [Level 5] It also requires an even greater approach from safety organizations and manufacturing companies.

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