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Section Editor: Craig M. Kessler, MD

Non-Anticoagulant Effects of Unfractionated and Low–Molecular Weight Heparins

Jeanine M. Walenga, PhD
Professor
Thoracic & Cardiovascular Surgery and Pathology
Cardiovascular Institute
Loyola University Medical Center
Maywood, Ill.

H&O How were non-anticoagulant effects of unfractionated and low–molecular weight heparins discovered?

JW Non-anticoagulant effects of unfractionated and low–molecular weight heparins (LMWHs) were discovered by clinical observation in patients suffering from cancer, inflammatory disorders, and infections when the patients showed improvement in terms of mortality, outcome, and responses. More recently, patients with diseases such as cancer and HIV are reported to gain benefit from heparins regardless of their antithrombotic effects. Anecdotal reports of a decrease in swelling in patients given heparin have been circulating for some time. Profibrinolytic, antiproliferative, and immunomodulatory effects of heparin were found in both animal and human studies after the dissipation of antithrombotic effects. For example, it was observed that heparin promoted greater blood flow than was expected in some studies. In clinical trials of the antithrombotic effects of heparin, unexpected antiangiogenic effects were observed in cancer patients who experienced longer survival than those who did not receive heparins. Due to cancer's heterogeneity, trials have been designed to focus on a single type of cancer, looking at survival times in patients treated with or without an LMWH. The original trials were designed to assess control of thrombosis, but trials today are assessing survival outcomes. Research into the antiangiogenic effects of LMWHs is somewhat further along than research into these agents' other potential non-anticoagulant effects because of the excitement about the possibility of using LMWHs in this setting. Although questions about dosing or which agent is best for which setting have yet to be elucidated, it is clear that these agents have antiangiogenic and anti-inflammatory properties.

H&O What are the mechanisms of the non-anticoagulant effects of heparins?

JW Heparins belong to the glycosaminoglycan (GAG) family, whose members have a wide structural diversity and thus a diverse range of actions, including regulation of cell growth, cell adhesion, cell morphology, lipid metabolism, and anticoagulant activities (against coagulation proteins and platelets). Heparin itself is a specific type of GAG. The precise mechanisms of the non-anticoagulant effects of heparins are not yet fully understood. Heparins bind to many different proteins, and it is theorized that by binding to, for example, vascular endothelial growth factor, heparins are able to suppress the mechanisms that produce tumor cells or blood vessels. Heparin probably has a regulatory effect on cell growth, but this hypothesis has yet to be confirmed. It is now well documented that heparin affects endothelial cells and releases tissue factor pathway inhibitor (TFPI), which helps to augment the anticoagulant properties of heparin itself. Heparin thus has direct effects as an anticoagulant and also indirect effects because it has activity on the endothelial system. In other words, TFPI can enhance the anticoagulant properties of heparin. Besides TFPI, several other endogenous substances are released from the non-anticoagulant components of heparins. These include the GAG heparan sulfate, nitric oxide, and prostacyclin. Moreover, the non-anticoagulant components of heparin can also complex with proteins to modify their actions.

In the natural setting, healthy endothelial cells line the blood vessels. Covering the surface of the endothelium are GAGs that act as receptors functioning as immobilized anticoagulants and helping to protect the cellular surface so that it remains antithrombotic. They also remove unnecessary thrombin from the blood system. Administration of heparin adds back to the body some of the natural product that the body uses constantly. Additionally, heparins bind to cytokines, which is related to the anti-inflammatory, immunomodulatory, and profibrinolytic effects that have been observed. Heparins thus take part in a process of cellular normalization and protection. In contrast, there are thrombin inhibitors or factor Xa inhibitors in development that focus on only one enzyme within the coagulation system; heparin affects many of the coagulation factors, platelets, and endothelial cell function. Heparin is polytherapeutic, with many physiologic effects. Its broad-based anticoagulation as opposed to inhibition of only thrombin, for example, is in my mind more efficient, especially when we consider its additional anti-inflammatory and immunosuppressive effects.

H&O Are there known drawbacks or reasons for caution in the non-anticoagulant uses of heparins?

JW Heparin is a heterogeneous mixture of different long- and short-chain sugar molecules, and the saccharide units within each chain are also heterogeneous. The properties of a full heparin, which include a propensity to induce bleeding as well as the non-anticoagulant effects, can enhance untoward effects in patients at risk of bleeding. For example, if more TFPI is released in the setting of high-dose heparin administration, which inhibits thrombin generation and affects platelets, it could cause bleeding. Researchers over the years have experimented with isolating different types of heparin chains. Some chains with only non-anticoagulant properties can be isolated, meaning that it is possible to remove the chains that cause bleeding.

There are other side effects associated with heparin. Use of heparin for anti-inflammatory purposes over many years could potentially cause osteoporosis. Some patients are more susceptible to heparin-induced thrombocytopenia than others, and the possibility exists that patients receiving heparin for non-anticoagulant purposes would be at risk of this side effect. Further research is required to determine which structural components of heparin cause the positive effects and which cause the negative effects and whether these components can be removed without compromising efficacy.

H&O What are the concerns with using heparin for its non-anticoagulant effects in a patient who is otherwise already receiving anticoagulation therapy?

JW Typically, a patient is receiving heparin anticoagulation therapy because he or she is at risk of thrombosis or is experiencing thrombosis. If this same patient is administered a heparin for its antiangiogenic properties, it is quite likely that an additive or synergistic bleeding effect would be induced. If a particular type of non-anticoagulant heparin with a reduced risk of bleeding could be used for its antiangiogenic property, it would be possible to use it in combination with another anticoagulant. It is necessary, in the setting of combination therapy, to understand each drug's risks and benefits as well as the possibility of augmenting the side effects of combined treatment. If more refined formulations of heparins can be developed that lessen their potential risks, combination therapy will become less risky.

H&O What trials are currently ongoing to research the non-anticoagulant effects of heparins?

JW Per se, there are no clinical trials focusing on the non-anticoagulant effects of heparins. However, heparins and LMWHs have been tested in such conditions as inflammatory bowel disease, fetal salvage in antiphospholipid syndrome, cancer, sepsis, and diabetic nephropathy.

The thrust is to develop non-anticoagulant forms of heparins and heparin-related drugs. Such heparin-like agents are danaparoid, dermatan, sulodexide, and an oral sulfomucopolysaccharide. It is likely that other non-anticoagulant forms of heparin-like drugs will be developed.

Suggested Readings

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