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Stanching the Action of Anticoagulants

Critical Need Exists for Heparin-Reversal Treatments with Minimal Side Effects

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Every day, surgeons are faced with the task of ensuring that their patients do not experience blood clotting during the invasive procedure. Clots can be potentially life-threatening, since they can lodge in the brain and cause a stroke, or in the heart and cause a heart attack, or in the lungs and compromise the ability to oxygenate blood.

The anticoagulant heparin is routinely used in certain acute surgical applications to prevent blood clots from forming during the procedure. Once surgery is complete, however, the action of heparin needs to be reversed in order to allow the patient to clot and heal normally.

A separate challenge involves the need to minimize the potential for blood clotting in patients outside the hospital setting, for longer term care. To this end, a class of substances known as low molecular weight heparins (LMWH) are prescribed for some patients in place of unfractionated heparin as a method of preventing clotting. They are given for chronic prophylaxis of thrombosis, after hip replacement surgery, after heart attacks, and in some cancer patients.

Clinical studies have revealed a 1% to 4% rate of major bleeding episodes in those patients using LMWH, with up to a 20% overall bleeding rate, particularly in certain patient populations.

Currently, protamine sulfate is the only agent available to reverse the action of heparin. Protamine binds to heparin to form a stable ion pair that does not possess anticoagulant properties; the complex of heparin and protamine is then removed by the reticuloendothelial system.

Despite the fact that it is the only clinical reversing agent available for heparin, protamine exhibits many limitations and potentially serious toxicities.

To begin with, protamine itself possesses anticoagulant properties, and can affect both fibrin clot formation and platelet aggregation in human blood—if it is administered in higher doses than needed, it may exacerbate bleeding in the patient. The dose may need to be carefully adjusted, such as with multiple administrations. This means that in clinical use, protamine may have to be given in several injections over time, with blood clotting tests done between the administrations, in an effort to reach but not exceed the required dose. This can make protamine complicated and expensive to administer.

Second, protamine is derived from an animal protein—salmon sperm—and may trigger allergic reactions, potentially life-threatening, in some patients. Additionally, manufacturing of a biologic derived from a natural source such as fish may be complicated, and can raise problems with quality control over the raw material.

Heparin itself is manufactured using animal parts as the raw material. In the case of heparin, most of this raw material comes from China. Recently there were significant problems with adulterated raw material and counterfeiting, with dangerous additives being added to the raw material that resulted in significant adverse reactions and patient deaths. A fully synthetic medical product can generally have much better control over the quality of the raw materials and ingredients.

Third, because protamine is a foreign animal protein, patients may develop an immune reaction to it by creating neutralizing antibodies to protamine. This can complicate subsequent administration of protamine for repeat procedures, in which case it either may not work, or may cause a potentially dangerous allergic reaction upon subsequent exposure.

Certain patient groups, such as diabetic patients receiving NPH (protamine-zinc), or males who have had vasectomies (because they may have pre-existing antibodies to sperm-derived products), may also be at greater risk of having an immune reaction to protamine and thus experience difficulties in receiving it.

Fourth, since protamine has poor fibrokinetics (it affects both fibrin clot formation and platelet aggregation in human blood), it can interfere with normal clot formation. Clots that are formed after protamine administration are considered structurally impaired, and lack the integrity of normal clots, meaning that such clots may break up and leak. Thus, there is a risk of recurrence of bleeding after administration of protamine.

This is often seen as post-operative bleeding after many procedures, which must be monitored to insure patients do not experience dangerous blood loss. In serious cases of post-operative

bleeding, re-operation may be necessary to find and stop the source of the bleeding.

Finally, protamine suffers from a lack of consistent activity against LMWH, and is not approved for this use. While it is sometimes used as a rescue agent of last resort in such cases, protamine is not generally clinically effective at reversing the risk of bleeding that is associated with LMWH use. Indeed, no clinically effective antidote for the LMWHs has ever been identified. Current treatments for bleeding associated with LMWH generally consist of transfusion, hospitalization, and surgery.

Given this situation, there is a need for a drug that is easier and safer to use than protamine for heparin reversal. There is also a significant need for a reversing agent for LMWH, for which none currently exists.

The search for alternatives to protamine is clearly an important one, but to date it has generated few successes, although [PolyMedix](#) just completed a Phase Ib study with PMX-60056, which acts as a universal anticoagulant reversing agent against both heparin and LMWH.

The most significant previous attempt to create a marketable anticoagulant reversal agent took place about two decades ago, when [Biomarin](#) developed a drug known as heparinase. Intended to cleave heparin, it actually worsened bleeding in some patients. The results of a study led by Duke University researchers in 2005 confirmed that heparinase is not a suitable replacement for protamine, and the compound was discontinued from development.

A search of the relevant literature reveals some additional attempts to identify alternatives to protamine, but little in the way of concerted efforts to develop them for market.

A 1995 study by Dehmer et al. assessed the reversal of heparin anticoagulation by recombinant platelet factor 4 (rPF4). After evaluating the safety and effectiveness of intravenous rPF4 to neutralize heparin anticoagulation, the authors concluded that, given in sufficient amounts, it could completely and rapidly reverse the anticoagulant effects of heparin. However, a study conducted the same year by Kurrek et al. concluded that rPF4 produces acute pulmonary hypertension in lambs.

In 1996, Kikura et al. examined the effectiveness of methylene blue, hexadimethrine, and vancomycin to neutralize heparin. They concluded that hexadimethrine could reverse heparin-induced anticoagulation after cardiopulmonary bypass as well as protamine, while methylene blue and vancomycin did not neutralize heparin in vitro.

A challenge as complex as the creation of a superior alternative to protamine will not be easy to overcome. However, given the widespread use of heparin and LMWH, and the need for a safer and more widely applicable solution than protamine to the problem of anticoagulant reversal, it is to be expected that exciting advances lie ahead.

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