Virtual Mentor
Ethics Journal of the American Medical Association
April 2005, Volume 7, Number 4

Clinical Pearl

Complications of Anticoagulation with Heparin

by Mahesh Krishnamurthy, MD, and Michael L. Freedman, MD

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are important, lifesaving pharmacotherapeutic agents for those with disorders such as coronary artery disease and other ischemic coronary events, atrial fibrillation, heart valve diseases, stroke, pulmonary embolism, and deep venous thrombosis. But there is a potential for many side effects with the use of these agents. Hence it is important to do a risk-benefit analysis before prescribing them to patients. The possible side effects of therapy should be told to the patients and their families before these agents are administered. Because heparins are usually given in life threatening situations where time is critical, the facts should be presented clearly with the risk-benefit analysis concisely conveyed to the patient and family. When complications do occur, physicians have to be candid with the patient and treat the complications rather than trying to conceal them.

UFH and LMWH therapy are associated with a high rate of drug-related problems and side effects due to either their inherent pharmacological properties or human errors. Thrombocytopenia, bleeding events, and osteopenia are the 3 most common drug-related problems associated with heparin and LMWH therapy. These side effects often complicate treatment and increase the overall cost of care. The Institute for Safe Medication Practices has classified both UFH and LMWH as high-alert drugs. Approximately 2.1 percent of the total records submitted to the MedMARx national error database were related to UFH; 4.5-5.5 percent of the reported errors were harmful [1].

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia with Thrombosis (HITT)

HIT occurs in 3 to 5 percent of patients who receive intravenous unfractionated heparin compared to the 0.5 percent incidence rate with subcutaneous LMWH, catheter flushes, and even the minuscule amounts of heparin that leach from coated catheters. HIT can precipitate an extreme prothrombotic diathesis known as HITT, resulting in venous or arterial thromboemboli in 50 percent of patients. http://archinte.ama-assn.org/cgi/content/full/164/18/1961 - REF-ICM30019-1#REF-ICM30019-1. Without prompt and effective treatment, likely outcomes are limb amputation in 10 to 20 percent of cases, death in 20 to 30 percent of patients, and residual deficits in survivors that can contribute to strokes, myocardial infarctions, and pulmonary emboli. When platelet counts decrease significantly (usually 50 percent of baseline), heparin should be stopped immediately, and, if anticoagulation is

necessary, direct thrombin inhibitors like lepirudin or argatroban should be started [2,3].

Suppose that a 68-year male is admitted to the intensive care unit with pneumonia and septic shock. He is started on antibiotics, IV fluids, and other supportive measures. He is also given subcutaneous heparin for prophylaxis against deep venous thrombosis. On the eighth day, he develops severe left lower extremity pain. His limbs become blue, and the dorsalis pedis pulse is not palpable. His platelet count drops from 220 000 on admission to 55 000. He is taken to the operating room for an amputation of the leg, below the knee.

This case demonstrates the phenomenon of heparin-induced thrombocytopenia with thrombosis (HITT) and illustrates the need to monitor platelet counts very closely during the course of heparin—even subcutaneous heparin—therapy. HIT can lead to HITT, which can cause severe harm. The early identification of HIT and subsequent termination of heparin therapy can prevent complications.

Hemorrhagic Complications with Heparins

The major complication of anticoagulant therapy is bleeding. LMWH is associated with less major bleeding than UFH. The ease of use, absence of mandatory laboratory monitoring, and clinical efficacy of LMWH have led to its widespread use for anticoagulation therapy in a number of disorders. LMWH is excreted entirely by the kidneys, and, accordingly, in the absence of data regarding safety, it should not be used in patients with compromised renal function. UFH, however, is rapidly metabolized by a saturable, zero-order mechanism, mainly by the reticuloendothelial system. Metabolism is followed by a slower first-order renal clearance. Less than 10 percent is excreted unchanged in urine. The mean half-life is dependent on the administered dose and is unchanged when renal function is normal.

Now, suppose that an 84-year-old female is admitted for shortness of breath. She is frail, weighing only 92 lbs. Routine labs reveal hemoglobin of 12.8 and a creatinine of 1.3, and she is found to have deep venous thrombosis of her right lower extremity. A perfusion scan of her lungs is consistent with a pulmonary embolism. She is started on low molecular weight heparin and other supportive measures. She improves but on the third day of treatment, develops severe hematuria and gastrointestinal bleeding; her hemoglobin falls to 8.6.

This situation demonstrates the drawbacks of using LMWH in patients with renal failure. It also emphasizes the need to calculate creatinine clearance (CrCl), rather than just serum creatinine in elderly and frail patients. The calculated creatinine clearance in this case is 21 ml/min. At such low ranges of creatinine clearance, LMWH can cause hemorrhaging and should not be used.

It is recommended that UFH be used to provide full anticoagulation therapy in patients with severe renal insufficiency. If LMWH is chosen, monitoring should be performed with therapeutic anti-factor Xa activity. The lowest ratio of CrCl levels for

patients in this indication category probably varies for different LMWHs, but a safe threshold is likely to be 30 mL/min.

When LMWH is used in patients with mild to moderate renal failure, anti-factor Xa levels should be tested to monitor therapy. This test should also be used when LMWH is administered to obese patients because they are more likely to receive inappropriate doses when weight-adjusted regimens are used.

When using UFH the following should be noted:

- There is an increased rate of major bleeding with intermittent intravenous (IV) heparin compared with continuous IV infusion; continuous IV heparin and subcutaneous heparin are associated with a similar amount of bleeding.
- The risk of heparin-associated bleeding increases with concomitant thrombolytic therapy or GP IIb/IIIa antagonists.
- Renal failure, patients aged over 70 years, and female gender have also been implicated as risk factors for heparin-induced bleeding.
- There is good evidence that comorbid conditions, particularly recent surgery or trauma, are important risk factors for heparin-induced bleeding [4,5].

When bleeding occurs with UFH therapy, protamine should be used to reverse the effects of heparin. However, protamine appears to neutralize only approximately 60 percent of the anti-factor Xa activity of LMWH.

Heparin-associated Osteoporosis

Heparin-associated osteopenia and osteoporosis are rare but potentially serious complications of heparin and LMWH therapy. Both are associated with long-term therapy (usually greater than 1 month) and often occur during pregnancy and the postpartum period when it can result in spontaneous fractures. Factors that contribute to development of these conditions are overactivation of osteoclasts by parathormone, decreased activity of osteoblasts, increased bone resorption as a result of abnormal collagen activation, and disturbances in vitamin D metabolism. Additionally, limited sun exposure during pregnancy and increased calcium demands during lactation can cause an osteoporotic state [6,7,8].

Imagine that a 31-year female with systemic lupus erythematosis and a history of 3 spontaneous abortions is diagnosed with antiphospholipid antibody syndrome. She is put on heparin therapy for the duration of her fourth pregnancy, after which she delivers a full-term healthy baby. During the postpartum period, she sustains a hip fracture after a trivial fall.

The hypothetical situation illustrates a typical scenario where long-term anticoagulation in pregnancy led to a fracture in the postpartum period. This result cannot be totally guarded against, but certain precautions can be taken. Adequate calcium and vitamin D supplementation is one potential prophylatic measure. It is also

of note that LMWH presents less risk for osteoporosis than UFH and should be preferred in this setting.

References

1. Niccolai CS, Hicks RW, Oertel L, Francis JL. Heparin Consensus Group. Unfractionated heparin: focus on a high-alert drug. *Pharmacotherapy.* 2004; 24(Pt 2):146S-155S.
2. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the seventh ACCP conference on antithrombotic and thrombolytic therapy. 2004;126(Suppl):311S-337S.
3. Rice L. Heparin-induced thrombocytopenia: myths and misconceptions (that will cause trouble for you and your patient). *Arch Intern Med*. 2004;164:1961-1964.
4. Levine MN, Raskob G, Beyth RJ, Kearson C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):287S-310S.
5. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):188S-203S.
6. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):627S-644S.
7. Ginsberg JS, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest.* 1998;114:524S-530S.
8. Wawrzynska L, Tomkowski WZ, Przedlacki J, Hajduk B, Torbicki A. Changes in bone density during long-term administration of low-molecular-weight heparins or acenocoumarol for secondary prophylaxis of venous thromboembolism. *Pathophysiol Haemost Thromb*. 2003;33:64-67.

Mahesh Krishnamurthy, MD, is a fellow in the Department of Geriatric Medicine at New York University Medical Center in New York.

Michael L. Freedman, MD, is a professor and the chief of the Department of Geriatric Medicine and director of The Diane and Arthur Belfer Geriatric Center at New York University Medical Center in New York.

Last updated: Mar 31, 2005