

Undisclosed Dangers of Heparin

A New Mass Tort on the Horizon?

by Neal Lewis and Daniel R. Lapinski

American history includes many notable products that were once thought to be beneficial but, over time and based upon an accumulating body of science, were found to be associated with shocking levels of injury and death. Tobacco and asbestos are two such products that quickly come to mind, where even after the great weight of research showed them to be highly lethal, manufacturers resisted disclosure of the dangers and long attempted to refute the science.

Heparin, a blood thinner administered to decrease the clotting ability of the blood,¹ may soon join the list of infamous products with risks of unrestricted uses far outweighing benefits. In early 2008, after Baxter Healthcare Corporation recalled several lots of its heparin products due to contamination, the drug was brought into the limelight.² In the months following the initial reports of contaminated heparin, personal injury and wrongful death cases began hitting both state and federal dockets. On June 9, 2008, the United States Judicial Panel on Multidistrict Litigation centralized contaminated heparin litigation pursuant to 28 U.S.C. § 1407 for coordinated or consolidated pretrial proceedings, and assigned the multi-district litigation (MDL) to the Honorable James G. Carr of the United States District Court for the Northern District of Ohio.³

On June 9, 2011, a Cook County, Illinois, jury awarded \$625,000 to the estate of a 63-year-old Chicago area man who had been administered contaminated heparin. The verdict was the first against Baxter and its supplier, Scientific Protein Laboratories.⁴ As of May 2, 2011, there were 264 contaminated heparin cases pending in the MDL.⁵ However, more significant than the hundreds of pending contaminated heparin cases, the publicity surrounding heparin appears to have uncovered another potential mass tort. The deaths and injuries alleged to have been caused by contaminated heparin pale in comparison to the estimated tens of thousands of deaths and injuries that apparently occur annually as a result of 'normal' heparin usage.

Heparin is administered to approximately 12 million patients each year.⁶ Of those 12 million patients it is estimated that up to five percent (600,000) develop heparin-induced thrombocytopenia (HIT).⁷ Of those patients who develop HIT, approximately half develop thrombosis, a life- and limb-threatening side effect that, if left untreated, can result in serious adverse events.⁸ Heparin-induced thrombocytopenia with

thrombosis is commonly referred to as HITTS.⁹ Without prompt treatment, the likely outcome is limb amputation in 10 to 20 percent, death in 20 to 30 percent, and residual deficits in survivors related to strokes, myocardial infarctions, and pulmonary emboli.¹⁰

Congress has entrusted the Food and Drug Administration (FDA) with the responsibility to ensure that drugs marketed in the United States are both safe and efficacious.¹¹ However, heparin has been marketed in the United States since the early 20th century,¹² long before FDA regulations on drug safety went into effect. As a result, heparin has never gone through the rigorous FDA regulatory approval process. The drug was originally produced from beef liver, but over the years the source of choice has become pig intestines, with production of raw heparin now largely performed in China.¹³ Given what is now known, it is doubtful heparin could obtain FDA approval, or at least an approval that did not come with instructions severely limiting its use.

Despite HITTS being perhaps the largest cause of drug-induced injury and death in modern times, heparin-related immune injuries are almost always under-diagnosed and untreated.¹⁴ This medical crisis has gained the increasing attention of the research community, with leading experts asserting that dangerous myths and misconceptions about HIT need to be corrected.¹⁵ Many of the myths and misconceptions in the medical community about heparin are perpetuated by the manufacturers' labeling and use instructions, which remain dangerously outdated and fail to disclose the risk of harm from unrestricted and routine use of heparin.¹⁶

In the 1970s and 1980s, a body of research had developed showing that heparin caused an adverse reaction in some patients, known as white clot syndrome (because of the white thrombus or clots observed in these patients). By the 1990s, the adverse reaction was

being called heparin-induced thrombocytopenia syndrome II (HITT), and the cause of the syndrome had gained consensus in the medical research community as an immunological response where antibodies form. With continued heparin therapy, those antibodies react with platelets (a coagulation component of blood), causing them to clump together and creating potentially lethal clots (thrombosis).

During the last decade, tests for heparin antibodies and protocols for identification of HITTS have gained attention in the medical research community. As the research on causes and responses to HITTS has advanced, so too has an ancillary body of research showing that developing heparin antibodies—even without the clotting syndrome of HITTS—could be linked to a greatly increased number of deaths and poor outcomes, particularly among cardiac patients. The increased rates of death and poor outcomes have been tied to circulating heparin antibodies caused by heparin exposure.¹⁷

While the research on this issue is compelling, this information has not been making its way to the average healthcare practitioner, with most of them continuing to believe heparin is relatively safe for most uses. Likewise, this information has not resulted in any changes to product labeling that would alert healthcare providers or the public to this extraordinary danger. Several pre-eminent research scientists have written about this knowledge gap and the possible lethal and adverse outcomes for patients.¹⁸

And, while the medical research community still publishes protocols on HITTS, the protocols can be best described as reactive medicine. Under currently accepted protocols, HITTS can only be 'diagnosed' once the syndrome has begun, meaning the circulatory system is already likely experiencing micro-thrombosis and injury at the cellular level.¹⁹

The protocols do not set forth any guidance on prevention, and are rather complicated and convoluted. Even detailed guidance in the protocols is often compellingly flawed. For example, the longer the HITTS syndrome goes unrecognized and untreated, the greater the likelihood of severe injury or death, and yet the protocols do not recommend any routine testing for heparin antibodies that could alert the practitioner to the potential for HITTS before the syndrome fully develops.²⁰

Nor do the research literature protocols give a reasonable schedule for platelet counts. The protocols rely heavily on a set drop in platelet counts for an initial suspicion of HITTS, and while almost all medical research scientists would agree that catching HITTS at the earliest stages is critical, it may evade detection during that all-critical early period for up to 24 hours, even where the recommended schedule for platelet counts in the protocols is followed exactly.²¹

Perhaps most distressing, current protocols give no consideration to preventing the high risk of injury and death associated with heparin antibodies that never develop into HITTS. While research literature strongly supports the contention that the immune response and development of circulating heparin antibodies, standing alone, puts patients at grave risk for death, injury and other poor outcomes, the research protocols remain silent. Research literature protocols, such as they are, have not been comprehensively placed into the heparin labeling, nor widely adopted by the healthcare community.²²

Product labeling instructions are one of the primary drivers of institutional decisions by the government, insurance industry and healthcare corporations. The aforementioned decisions affect the flexibility of the practitioner to order tests or alternative medicines that may be warranted by medical research.

FDA regulations require manufacturers

to update the FDA with major research developments about the risks of drugs they produce, and as the United States Supreme Court has made clear, a plaintiff's state law rights and the drug manufacturers' state law duty to issue current and adequate warnings are preserved under the FDA regulatory scheme.²³ Despite this, due to the lack of pertinent information in product labeling and instructions, many of the necessary tests and alternative medicines have been administratively deemed unnecessary.

Using pharmaceutical industry and research statistics, it can be interpolated that the unrestricted use of heparin annually causes 100,000 HITTS-related deaths and severe injuries. This figure does not include the known increase in injuries and deaths from isolated heparin antibodies (*i.e.*, heparin antibodies not progressing to defined HITTS).²⁴ However, these injuries and deaths from both HITTS and isolated heparin antibodies remain hidden because the injuries mimic the symptoms, conditions and outcomes already expected in patients, meaning the vast majority of heparin injuries and deaths routinely go unnoticed and undocumented by most healthcare providers.²⁵

As more has become known about the high risk of death and injury from heparin, and as many alternative blood thinners come to market, the more obvious it becomes that continued uses of heparin in a broad area of specialties should be reevaluated.

While commentators can be found who will opine that heparin injuries are over-diagnosed, contemporary medical research continues to show that a staggering number of heparin-related deaths and injuries remain hidden from both the medical and public view.²⁶ As recently as 2008, a retrospective study of thousands of patients from numerous healthcare facilities found that diagnostic criteria suspicious for HITTS was rarely given any consideration (less than

10 percent of the time), and even when the criteria was evaluated, the response was almost always inappropriate.²⁷ A review of the manufacturing labeling, even with recent updates, reveals the cause of this continued lack of an informed medical community, with little being done in the labeling to alert the medical profession to the risks from heparin and the need to restrict its use.

To date, approximately 20 cases have been filed throughout the country against heparin manufacturers, asserting injuries and deaths due to defendants' failure to adequately warn of the risks associated with the drug. In defending the litigation, heparin manufacturers have argued that product labeling and instructions are adequate, and that the risks associated with HITTS are fully disclosed. However, as literature continues to mount, and public awareness of the hazards of heparin increases, it appears increasingly likely that litigation will burgeon into a mass tort. ♪

Endnotes

1. See Updated Questions and Answer on Heparin Sodium Injection (Baxter) (6/18/2008), www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112606.htm.
2. See Baxter's Multiple-dose Vial Heparin Linked to Severe Allergic Reactions FDA Advises Health Care Practitioners to Switch Suppliers and Limit Use of Drug Until Problem Identified, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116858.htm. See also Updated Questions and Answer on Heparin Sodium Injection (Baxter), www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112606.htm.
3. See *In re: Heparin Products Liab. Litig.*, Case No. 1:08-60000 (N.D. Ohio), MDL Docket No. 1953.

4. See http://articles.chicagotribune.com/2011-06-09/business/chi-baxter-loses-first-heparin-case-20110609_1_baxter-heparin-animal-like-substance-scientific-protein-laboratories.
5. See www.jpml.uscourts.gov/Pending_MDJ_Dockets-By_District-May-2011.pdf.
6. Lawrence Rice, Heparin-Induced Thrombocytopenia, Myths and Misconceptions (That Will Cause Trouble for You and Your Patient), *Arch of Intern Med.* 2004; 164: 1961-1964.
7. Robert Levine, Finding Haystacks Full of Needles From Opus to Osler, *Chest* 2005; 127:1488-1490.
8. Theodore Warkentin and John Kelton, A 14-year Study of Heparin-induced Thrombocytopenia, *Am J Med.* 1996; 101:502-507. See also HIT Consortium Issues Consensus Recommendations to Improve Patient Care and Guard Against Limb-and-Life Threatening Condition, *PRNewswire-FirstCall*, Feb. 16, 2005.
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10. Theodore Warkentin and John Kelton, A 14-year Study of Heparin-induced Thrombocytopenia, *Am J Med.* 1996; 101:502-507. See also Lawrence Rice, et al., Heparin-induced Thrombocytopenia/Thrombosis Syndrome: Clinical Manifestation and Insights [abstract], *Blood*, 1986; 68 (suppl 1): 339a.
11. 21 U.S.C. § 393(b)(1).
12. See Updated Questions and Answer on Heparin Sodium Injection (Baxter) (6/18/2008), www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112606.htm.
13. *Id.*
14. HIT Consortium Issues Consensus Recommendations to Improve Patient Care and Guard Against

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15. Robert Levine, Finding Haystacks Full of Needles From Opus to Osler, *Chest* 2005; 127:1488-1490.
 16. R. Taylor Williams, Lakshmi Damaraju, Mary Ann Mascelli, Elliot Barnathan, Robert Califf, Maarten Simoons, Efthymios Deliargyris, and David Sane, Anti-Platelet Factor 4/Heparin Antibodies, An Independent Predictor of 30-day Myocardial Infarction After Acute Coronary Ischemic Syndromes, *Circulation* 2003, 107:2307.
 17. *Id.*
 18. *Id.*
 19. See Theodore Warkentin and Andreas Greinacher, et al., Treatment and Prevention of Heparin-Induced Thrombocytopenia American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), *Chest* 2008;133:341S-380S
 20. Lawrence Rice, Walid Attisha, Alane Drexler, and John Francis, Delayed-onset Heparin-induced Thrombocytopenia, *Ann. Intern. Med.* 2001; 135:502-506.
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 22. See *Wyeth v. Levine*, 555 U.S. 555, 129 S. Ct. 1187, 1195-96 (2009).
 23. R. Taylor Williams, Lakshmi Damaraju, Mary Ann Mascelli, Elliot Barnathan, Robert Califf, Maarten Simoons, Efthymios Deliargyris, and David Sane, Anti-Platelet Factor 4/Heparin Antibodies, An Independent Predictor of 30-day Myocardial Infarction After Acute Coronary Ischemic Syndromes, *Circulation*, 2003, 107:2307.
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