Unfractionated Heparin: Focus on a High-Alert Drug

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Unfractionated heparin (UFH) is associated with a high rate of drug-related problems due to either its inherent pharmacologic properties or an extension of these properties often caused by medication errors. The drug-related problems associated with UFH can significantly hinder the success of therapy and negatively affect the overall cost of care. Unfractionated heparin has been classified as a high-alert drug by the Institute for Safe Medication Practices. Approximately 2.1% of the total records submitted to the MedMARx national error database were related to UFH; 4.5–5.5% of these errors reported were harmful. With this high potential for error, it is essential that all health care providers adopt a collaborative or systems approach to identify solutions to reduce the occurrence of these medication errors. The Joint Commission on Accreditation of Healthcare Organizations has published national patient safety goals for improving the safety of patient care, many of which are applicable to UFH therapy. Unfractionated heparin drug-related problems not necessarily related to medication errors include heparin-induced thrombocytopenia, bleeding events, and osteopenia. Heparin-induced thrombocytopenia is a serious complication of heparin therapy and remains seriously undiagnosed. Bleeding events often occur with therapeutic as well as prophylactic UFH administration even when monitoring indexes are within the therapeutic range. However, due to the variability associated with UFH monitoring methods, definitive guidelines are lacking to assist in avoiding such serious events. Osteopenia has been associated with long-term UFH therapy; one third of patients experience reductions in bone density, potentially leading to fractures. Today, safer alternative anticoagulation therapies are available, such as the low-molecular-weight heparins. When compared with UFH, these alternative therapies provide equivalent or superior efficacy for numerous indications.

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Drug-related problems significantly affect the net benefit of drug therapy and frequently result in negative clinical and economic outcomes.[1] Based on 2000 data, drug-related problems account for 69% of the total cost of hospitalization or $121.5 billion annually.[2] A drug-related problem may be due to an agent's inherent pharmacologic effect or an extension of this effect as a result of overdosage, subtherapeutic dosage, or failure to receive a drug for a variety of reasons.[1]

Unfractionated heparin (UFH) has been commercially available since the 1940s and is one

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Table 1. Frequency of All Nonharmful and Harmful Errors Reported to MedMARx from 1999–2002 Related to UFH

UFH Errors Reported	No. (%) of All Errors Reported			
	1999	2000	2001	2002
Nonharmful	173 (3.2)	1063 (3.0)	2201 (2.5)	3545 (2.3)
Harmful	11 (4.5)	59 (5.0)	130 (5.5)	139 (4.6)
Totals	184	1122	2331	3684

UFH = unfractionated heparin.
From references 9–12.

of the most widely prescribed parenteral drugs in modern medicine for millions of patients annually. For many years intravenous UFH has been a key therapeutic agent in the treatment of thrombotic conditions such as deep vein thrombosis, pulmonary embolism, and acute coronary syndromes.[3] However, UFH is associated with a high rate of drug-related problems due to its extensive use, complex pharmacologic profile, and high potential for medication errors. The frequency of these drug-related problems significantly hinders the success UFH therapy and negatively affects the overall cost of care.

UFH Medication Errors: In the Top 10

Results of the Institute of Medicine's 1999 report suggest that medical errors account for 44,000–98,000 deaths/year.[4] The estimated total cost of medical errors in the United States is $17–29 billion annually. Medication errors are perhaps the largest subset of medical errors. A medication error, as defined by the National Coordinating Council for Medication Error Reporting and Prevention, is any preventable event that may cause or lead to inappropriate drug use or patient harm while the drug is in the control of the health care professional, patient, or consumer.[5] According to information submitted to the Food and Drug Administration's Adverse Event Reporting System, during 1993–1998, the most common types of medication errors leading to patient deaths were improper dosing of the intended drug and administration of an incorrect drug.[6]

Over the years, intravenous UFH therapy has been associated with a high error rate, largely due to the need for numerous dosage adjustments and frequent laboratory monitoring. Weight-based dosing protocols have been used in an attempt to refine UFH dosing and monitoring; however, the adoption of numerous protocols within a single institution merely adds to the dosing and monitoring confusion. In addition to these challenges, the use of abbreviations, dosage and rate calculations, multiple-solution concentrations, and intravenous delivery pumps further increase the risk of medication errors. Although frequently prescribed, UFH remains a difficult drug to manage from the medical, nursing, pharmacy, and laboratory perspectives.

The Institute for Safe Medication Practices (ISMP) has classified UFH as a high-alert drug, which is defined as a drug widely used in the health care setting that has a high risk of patient injury when administered incorrectly.[7] A nursing and pharmacy survey conducted by the ISMP revealed that over 80% of respondents also considered UFH a high-alert drug and had special precautions in place for its use within their respective institutions.[8]

MedMARx is an Internet-accessible, anonymous medication error database operated by the United States Pharmacopeia (USP). The USP publishes annual data summaries of medication error events voluntarily reported to this database. In summaries of the errors submitted, UFH was the third most commonly reported product in 1999, second in 2000, fourth in 2001, and fifth in 2002. Together, four summaries represent over 7300 medication error events involving UFH. This is equivalent to about 2.1% of the total records submitted, of which 4.5–5.5% were harmful (Table 1).[9–12]

Further analysis showed that UFH medication errors resulting in harm consistently ranked as either the second or third most commonly reported products from 1999–2002, positioned closely to other high-alert products such as insulin and morphine. Unfractionated heparin reportedly was involved with a patient's death in both 2001 and 2002.[11, 12] In addition, in 2002, UFH was the most frequently reported drug when the error was due to improper dosage or quantity (Table 2).[12]

Errors associated with UFH have been consistently reported in other studies conducted

Table 2. Most Frequently Reported Drug Products and Errors Due to Improper Dosage or Quantity in 2002

Error Category	Product	No. (%) of Errors
All error categories (n=44,593)	UFH	1275 (2.9)
	Insulin	1220 (2.7)
	Morphine	959 (2.2)
Most harmful types of errors (n=856)	UFH	81 (9.5)
	Morphine	79 (9.2)
	Insulin	65 (7.6)

UFH = unfractionated heparin.
From reference 12.

by the USP. In a focused review of emergency department medication errors conducted in 2001 by the USP using MedMARx data, UFH was again the leading drug associated with dosing errors.[11] In the same study, UFH ranked third for errors of omission and fourth for actual prescribing errors. In addition, UFH was a leading drug involved in improper dosage or quantity errors in a review of medication errors in the day-surgery setting.[13] For medication errors occurring in the post-anesthetic care unit, UFH was implicated with improper dosage or quantity errors (when invasive flush line bags were replaced with concentrated heparin solution) and omission errors.[14] For errors occurring during surgery, UFH has been associated with omissions, unauthorized drug, and improper dosage- or quantity-type errors.[15]

Reducing Intravenous UFH Errors

An investigative report published in 2000 described the extent of medication errors in health facilities today and helped serve as a catalyst for efforts to improve patient safety.[16] This report strongly suggested that nurses are at fault for causing poor patient outcomes due to issues involving incorrect drug delivery and administration. However, closer review revealed that many medication errors are attributed to a lack of effective safety systems designed to reduce the risk of an error event. In a typical hospital setting, drug orders proceed through a series of actions, such as prescribing, transcription, documentation, and dispensing, before administration of the drug at the bedside.

A review of 731 patients receiving therapeutic UFH found that approximately 92 steps were required to reach completion of the first dosage adjustment.[17] Most of the steps provided no prompt for the next step.

Such a process is opportune for error. As a result, many patient safety experts emphasize the need to evaluate problems from a systems approach, not one based on individual actions, and formulate solutions accordingly. Because nurses function at the level of providing direct patient care, they are easily singled out as the primary agents of medication errors. However, as emphasized in the Institute of Medicine report,[4] it is essential that all health care providers adopt a collaborative approach to identify solutions and not focus on who is to blame.

In general, new approaches to prevent medication errors and enhance patient safety are under way and frequently use solutions based on a systems approach rather than focusing on one aspect of patient care. Developing institutional standards and achieving institutional goals for improved patient safety can be a constant challenge; however, barriers to success can frequently be overcome by working collaboratively with an interdisciplinary team of professionals.[18] In addition, organizations focusing on patient safety can offer assistance in reaching these goals.

For example, the USP has included the following observations in the MedMARx 2002 data summary, based on the MedMARx database records[12]:

1. Technology has the potential to reduce many types of errors as well as the potential to create new errors. Implement with care.
2. Abbreviations, acronyms, or symbols frequently are associated with medication errors.
3. High-alert drugs consistently remain the most problematic products involved in medication errors.
4. The intravenous route of administration for drugs often results in the most serious medication error outcomes.

These observations are intended to generate discussion and promote action among health care providers with the primary goal of developing a safer institutional drug use system. Since 2002, the Joint Commission on Accreditation of Healthcare Organizations has required health care organizations to address national patient safety goals for improving the safety of patient care as part of the accreditation process.[19] A few of the 2004 goals are discussed in the following sections, with applications to UFH therapy.

Improve the Effectiveness of Communication Among Care Givers

In brief, this goal requires implementation of a process for verifying verbal or telephone orders and standardizing or eliminating the use of

abbreviations, certain acronyms, and symbols. Intravenous UFH infusions require frequent adjustments in response to periodic blood tests (activated partial thromboplastin time [aPTT]). In some circumstances, telephone orders from physicians to nurses are common. Implementing procedural steps to verify the complete and accurate UFH order when taken by telephone can reduce errors associated with this drug.

Relative to UFH use and based on collected data, the USP recommends that organizations employ preprinted standard order forms that have the institution's approved UFH dosing nomogram(s) to enhance communication among care givers involved with this therapy. These order forms should clearly identify the indication, prescriber, patient, patient's weight (accurately expressed in kilograms), patient's allergies, and target therapeutic value. In addition, spelling out "units" avoids the ambiguity of abbreviations and further reduces the opportunity for error. However, unfamiliarity with these preprinted orders and the UFH dosing nomograms, as well as the presence of several nomograms, can complicate an already error-prone process for all care givers involved. Limiting the number of standard order forms or nomograms within an institution will reduce errors.

Another method to improve communication among care givers is the use of patient-specific anticoagulation flow sheets. This documentation aid can help the prescriber quickly evaluate UFH therapy. It also can provide other staff members with a central place to record UFH treatment details, such as new physician orders, dosages administered, flow rate changes, laboratory values, and adverse events.

Improve the Safety of Using High-Alert Drugs

Policies and procedures adopted by a specific facility and supported by the medical, pharmacy, and nursing staffs can greatly improve UFH safety. These policies and procedures should mandate provision of targeted education programs to all health care practitioners involved with UFH use. A pharmacist's participation in staff education and training to review and teach the facility's protocols associated with UFH use can be very effective.

Technology allows for participation of several heath care practitioners in drug safety initiatives. For example, implementation of a patient-profile interface with automated dispensing cabinets located on nursing units efficiently brings pharmacy into the process. Before drug retrieval and administration, orders entered in the profiling system are reviewed and verified by a pharmacist. Further deployment of computer networks in hospitals provides the ability to have laboratory results such as aPTTs readily available for a pharmacist's review. Availability of computerized UFH dosing programs, or actual dosing charts on the patient care units, can reduce errors related to miscalculation of infusion rates. However, the staff administering UFH should still have documented competency in the actual performance of these routine calculations even when a computer program is available. In addition, appropriate independent double checks with other licensed professionals can reduce variances in dosing calculations and subsequent administration.

The USP suggests that technology also be enabled to print contraindications and other alerts on computer-generated drug administration records to warn care givers of a potential danger. Computer-generated labels affixed to UFH solutions should provide the required information and be readily understood by all health care providers. Also, only commercially available UFH solutions should be stocked, with standardized concentrations, and floor stock should be minimized where appropriate.

Improve the Safety of Using Infusion Pumps

Medication errors with intravenous infusions are generally associated with significant potential for harm. In 2002, MedMARx documented that 8.7% of cases involving infusion pumps resulted in some level of patient harm.[12] The drug-related problems linked to intravenous infusion devices are most often due to incorrect programming of the pump, resulting in an improper dosage or quantity error. Institutions can comply with this safety standard through the use and maintenance of infusion pumps with free-flow protection features. Compliance can be further enhanced through implementation and consistent documentation of procedural steps for safe operation of infusion pumps, such as maintenance of audible alarm systems.

In consideration of new advances in patient safety, "smart pumps" represent the next generation of infusion devices.[20] According to the ISMP, these devices are setting a new standard for intravenous drug administration. The smart pump is expected to reduce medication errors through innovative technology that integrates

institution-specific comprehensive drug libraries, usual drug concentrations, dosing units (e.g., micrograms/kilogram/minute, units/hour), and dose limits. These new infusion devices perform a "test of reasonableness" to ensure that information programmed into the pump coincides with preestablished institutional guidelines before the infusion is started.

In summary, medication errors are the cause of many drug-related problems that lead to numerous deaths each year and place an additional economic burden on health care systems. The process for using intravenous UFH is very complex and leads to numerous error opportunities for all involved. Effective safety standards for UFH therapy require institutions to recognize the scope of the problem and be willing to implement a systems approach for problem resolution.

One of the most significant barriers to reducing errors in health care is the "blaming culture."[21] Medication error reporting programs and targeted education initiatives to promote understanding of factors, not individual performances, are optimal mechanisms to reduce errors. Finally, using multidisciplinary teams to drive change at all levels of patient care will reduce errors throughout the process.

Drug-Related Problems: Bleeding and Beyond

Unfractionated heparin is associated with a number of drug-related problems, such as heparin-induced thrombocytopenia (HIT), bleeding complications, and osteopenia. The most serious potential UFH-associated drug-related problem is the prothrombotic disorder HIT; its primary feature is thrombocytopenia due to antibody-mediated platelet aggregation. Bleeding complications are the most frequently reported UFH-associated drug-related problem. These events often complicate and reduce the overall success of therapy. Finally, osteopenia, a drug-related problem primarily related to long-term UFH treatment, has been reported most often with UFH for management of venous thromboembolic events during pregnancy.

Heparin-Induced Thrombocytopenia

The reported frequency of HIT varies widely but is reportedly 1–3%.[22] The main reasons for variable estimates of frequency, especially in the earlier literature, are the use of different definitions of thrombocytopenia and failure to use sensitive laboratory methods to confirm the diagnosis. The pathophysiology of HIT is based on the

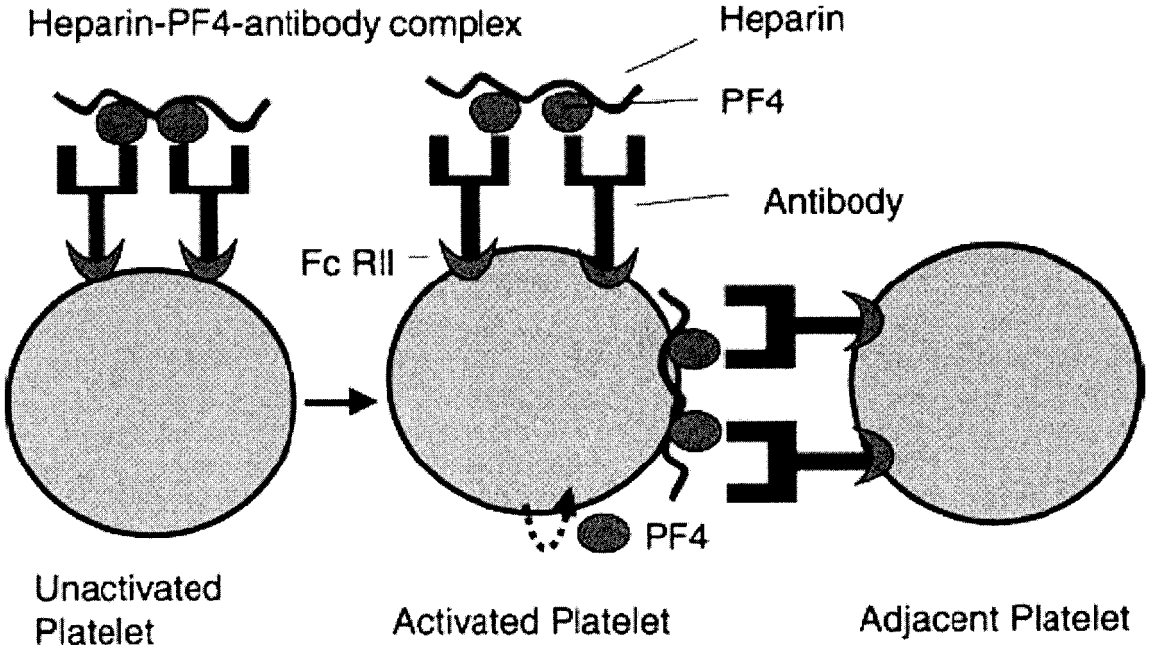

Figure. 1. Pathophysiology of heparin-induced thrombocytopenia (HIT). An antibody is produced that reacts with the complex formed by heparin and platelet factor 4 (PF4) released from activated platelets. These antibody-antigen complexes then bind to the platelet through its Fc receptors (FcγRIIa). Cross-linking the receptors leads to platelet activation and release of PF4 from the α-granules. The released PF4 reacts with heparin to form heparin-PF4 complexes on the platelet surface, which serve as additional sites for HIT antibody binding. The free Fc domains of the attached antibodies can then cross-link Fc receptors of a neighboring platelet. Adapted from reference 25.

production of an antibody to the complex formed by heparin and platelet factor 4 released from activated platelets.[23] Immunoglobulin-G forms of the platelet factor 4 antibody bind to the platelet through its Fc receptors (FcγRIIa).[24] Occupation of adjacent receptors causes intense platelet activation, with the release of highly procoagulant microparticles and, ultimately, intravascular thrombin formation (Figure 1).[25]

Because of the need to mount an immune response, HIT typically appears 4–10 days after the start of heparin therapy.[26] However, some cases may occur much sooner after heparin exposure. These so-called rapid-onset cases are due to the presence of an existing circulating heparin and factor 4 antibody.[27] Because these antibodies are usually transient, 90% have disappeared from circulation within 90 days. Thus, rapid onset of HIT typically is associated with heparin exposure in the recent past. A few cases appear as delayed-onset HIT, which may manifest itself 2–6 weeks after heparin therapy.[28, 29]

The risk of HIT is greatest with UFH. Bovine heparin appears to be more immunogenic than the porcine form.[30] Low-molecular-weight heparins (LMWHs) carry approximately one tenth the risk of HIT development, but they inevitably cross-react with the heparin–platelet factor 4 antibody and are contraindicated for treatment in patients with HIT. Very low-molecular-weight derivatives, such as pentasaccharides (e.g., fondaparinux), do not appear to cross-react, and preliminary reports indicate their successful use in patients with HIT.[31] Danaparoid, a heparinoid, cross-reacts in laboratory test systems but has been used for treatment without negative effects in many patients.[32] However, danaparoid is not available in the United States. Nonheparin anticoagulants, such as direct thrombin inhibitors, do not elicit formation of the heparin–platelet factor 4 antibody and are the treatment of choice.

Heparin-induced thrombocytopenia is a clinicopathologic syndrome in which the patient has both clinical and laboratory evidence of the condition.[33] A clinical diagnosis of HIT is suggested by the observation of a falling platelet count, with or without venous or arterial thrombosis, in a patient currently or recently receiving heparin therapy.[34] The platelet count falls within correct temporal aspects consistent with HIT after approximately 4–10 days of UFH therapy in patients not previously exposed to heparins, or within hours to days in patients exposed to UFH in the recent past. This is a decrease in the platelet count of more than 30–50% from baseline, or a platelet count of 50 x 10^3/mm^3 or less in patients with or without new thrombosis, and/or the development of new thrombosis in the presence of UFH or LMWH.

Less common signs are anaphylaxis after a heparin bolus, pain and swelling at the UFH injection site, and adrenal hemorrhagic infarction.[35] Development of skin necrosis in a patient who recently started receiving warfarin therapy may also herald the onset of HIT.[36] Because HIT can appear in several diverse ways, broad inclusion criteria are necessary to ensure that the diagnosis is not missed. On the other hand, this definition may involve many patients whose thrombocytopenia or thrombosis developed for other reasons, and they do not have the HIT syndrome. Heparin-induced thrombocytopenia may be difficult to diagnose in some patients; careful consideration of the pretest probability that a patient actually has HIT is useful.[33]

Laboratory tests for HIT are not 100% sensitive or specific, thus the diagnosis of HIT still rests primarily on clinical grounds. Nevertheless, subsequent confirmation or exclusion of the diagnosis through specific laboratory tests for the heparin–platelet factor 4 antibody is important and should be performed. Although the enzyme-linked immunosorbent assay (ELISA) for heparin–platelet factor 4 antibody is probably the most widely used test due to its technical simplicity, functional assays such as serotonin release, platelet aggregation, or flow cytometry have a higher specificity for clinical HIT.[37, 38] The ELISA test for heparin–platelet factor 4 antibodies may be positive in patients who do not have clinical HIT. For example, asymptomatic antibodies are produced in about 50% of patients undergoing cardiac surgery. Of interest, mounting evidence indicates that patients who produce heparin–platelet factor 4 antibodies have a higher risk of cardiovascular death, even in the absence of clinical HIT.[39]

The three key elements in managing HIT are stopping UFH therapy, starting treatment with an alternative anticoagulant, and avoiding primary management with warfarin or platelet transfusions. Heparin therapy should be stopped at the first sign of HIT, without waiting for a laboratory test result to confirm the diagnosis. Recognizing all sources of heparin is especially important, since failure to do so can cause HIT to continue, with potentially catastrophic consequences. Stopping heparin therapy alone, however, is not an adequate treatment for HIT,

Table 3. Relevant Characteristics of Argatroban and Lepirudin

Characteristic	Argatroban	Lepirudin
FDA approved for HIT dosing	Yes	Yes
Dosage	2-µg/kg/min continuous infusion	0.4-mg/kg bolus followed by 0.15-mg/kg/hr continuous infusion, or 0.1 mg/kg/hr in isolated HIT
Thrombin binding	Univalent	Bivalent
Half-life (min)	39–51	78
Antidote available	No	No
Route of elimination	Hepatic	Renal
Effect on INR	Substantial	Minimal

FDA = Food and Drug Administration; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio.
Adapted from reference 34.

which is a highly procoagulant condition.[40] Left untreated, more than 50% of patients with isolated HIT (thrombocytopenia but no evidence of thrombosis at diagnosis) will develop a clot within the next 30 days.[37]

Because this procoagulant condition leads to uncontrolled thrombin generation, the most appropriate therapy is a direct thrombin inhibitor. In the United States, two such agents are approved for this indication: lepirudin and argatroban (Table 3).[34] Lepirudin, a derivative of hirudin, is a bivalent thrombin inhibitor binding tightly to the catalytic site and the exocite of thrombin.[34, 41] Argatroban, derived from L-arginine, is a monovalent thrombin inhibitor binding only to the thrombin active site.[34, 42] Both agents have the ability to inhibit clot-bound and soluble thrombin and do not cross-react with heparin-induced antibodies. Because the two agents have different routes of elimination, lepirudin requires adjustment in patients with renal disease, and argatroban should be administered with caution in patients with hepatic impairment.[41, 42] Bivalirudin is a bivalent direct thrombin inhibitor widely administered during percutaneous coronary intervention.[43] Off-label experience is growing for its role in management of HIT.

Warfarin should not be used as primary treatment due to a high risk of warfarin-induced skin necrosis if given to a patient with active HIT. It is recommended that warfarin not be introduced until the platelet count has returned to normal. Even then, it is preferable to introduce the oral anticoagulant cautiously and not to administer a loading dose. Finally, spontaneous bleeding is uncommon in patients with HIT. Thus, platelet transfusions are not required; in fact, they are contraindicated since they may contribute to the thrombotic risk.[26]

Heparin-induced thrombocytopenia is a potentially serious complication of heparin therapy. The condition is associated with variable thrombocytopenia and extremely high risk of thrombosis. Despite its clinical importance, HIT remains seriously undiagnosed. Most cases occur after treatment with UFH; thus, a significant reduction in therapy with this anticoagulant would be reflected in a marked reduction in the frequency of clinical HIT. Because of the growing evidence that generation of heparin–platelet factor 4 antibodies is not necessarily benign, even in the absence of clinical HIT, a reduction in UFH administration also may improve patient outcomes.

Bleeding Complications

In pharmacologic terms, the bleeding potential of UFH is due to its ability to inhibit blood coagulation, impair platelet function, and increase capillary permeability.[44] Unfractionated heparin is prescribed in therapeutic dosages to treat acute venous thrombosis, and at this time no randomized venous thromboembolism (VTE) trials have compared rates of bleeding events between different UFH treatment dosages. However, a subgroup analysis of completed VTE studies suggests a potential association between the anticoagulant response (aPTT) to the prescribed dosage and the bleeding rate; when the in vitro test of coagulation is excessively prolonged, bleeding appears to be more likely. However, important bleeding also can occur when the aPTT is in the therapeutic range. Thus, due to the complex pharmacokinetics of UFH, variability of the aPTT assay, and lack of clinical evidence, definitive guidelines for avoiding bleeding events with various therapeutic UFH

dosing are not available.

Clinical trials evaluating intravenous UFH for treatment of VTE demonstrate that the rate is 0–7% for major bleeding and 0–2% for fatal bleeding.[44] A retrospective review of routine patient care published in 2000 found a 4% occurrence of major hemorrhage in 424 patients receiving intravenous UFH for treatment of VTE; one hemorrhage was fatal.[45] Another retrospective study, published in 2003, evaluated 311 patients who had received intravenous UFH for VTE management, cerebral arterial thrombosis, or peripheral arterial thrombosis.[46] During the course of therapy, 4.8% of the patients sustained a major hemorrhage.

The LMWHs have simplified treatment of VTE due to their ease of administration, standard dosing, and lack of need for routine monitoring. Many studies have evaluated whether the LMWHs are as effective and safe as traditional intravenous UFH therapy. Meta-analyses of these studies have produced varying results ranging from superior efficacy and safety of LMWHs to trends favoring LMWHs in comparison with UFH. A review of 13 studies compared intravenous UFH and LMWHs for management of VTE.[47] Overall, trends favored LMWH in terms of major bleeding. However, when inpatient administration of LMWH and intravenous UFH were specifically evaluated, the frequency of major bleeding was significantly higher for intravenous UFH ($p<0.01$). A meta-analysis based on 11 clinical trials compared intravenous UFH and LMWH for treatment of VTE.[48] In terms of major bleeding, the odds ratio (OR) favored LMWH for this safety outcome when a fixed-effects model was used (OR 0.57, 95% confidence interval [CI] 0.33–0.99, $p=0.047$).

A number of trials have evaluated UFH for management of acute coronary syndromes. In the patients studied, reported rates of major bleeding for intravenous UFH during the first 8 days of therapy were 0–6.3%.[44] In studies comparing intravenous UFH with LMWHs in patients with unstable coronary artery disease, such as the Thrombolysis in Myocardial Infarction (TIMI) 11B[49] and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trials,[50] the difference in major bleeding between groups was not significant. Similar results were demonstrated in the third Assessment of the Study and Efficacy of a New Thrombolytic Regimen (ASSENT-3).[51] This trial compared the safety and efficacy of full-dose tenecteplase-enoxaparin combination with standard full-dose tenecteplase plus UFH in patients with ST-segment elevation myocardial infarction. The differences in major bleeding and blood transfusions between enoxaparin and UFH were not significant.

Low-dose UFH is administered subcutaneously for prevention of VTE in medical and surgical patients. The most commonly prescribed regimens are subcutaneous UFH 5000 U twice/day and 3 times/day. The efficacy of the twice-daily regimen in populations at risk has been questioned. A meta-analysis of randomized VTE prevention trials in medical patients evaluated eight studies that compared LMWH with UFH.[52] The results demonstrated a significant reduction in the risk of major bleeding with LMWHs (risk ratio 0.48, 95% CI 0.23–1.0, $p=0.049$).

In terms of general surgery prophylaxis, a review of 59 trials included 51 that compared LMWHs with UFH.[53] Analysis of these head-to-head comparison trials found that in patients receiving UFH, the rate of major bleeding and wound hematoma was 3.2% and 6.1%, respectively. Identified trends suggested a reduction in risk of major bleeding, total bleeding, and wound hematomas with LMWHs. More specifically, this analysis concluded that low prophylactic doses of LMWH ($\leq$ 3400 antifactor Xa units) appear to be safer than UFH.

Osteopenia

Osteopenia occurs when the rate of bone synthesis is lower than the rate of bone lysis. Technically, osteopenia is defined as bone density 1–2.5 standard deviations below the bone density of a healthy young adult.[54] A person with osteopenia is at risk of developing osteoporosis, which is characterized by a greater loss of bone mass and disturbances of the microarchitecture of the bone tissue.[52] There are many risk factors for osteopenia, and one in particular is long-term treatment with UFH.

One third of patients receiving long-term UFH therapy have reductions in bone density leading to osteopenia.[55] Long-term UFH therapy leads to trabecular bone loss, not only by increasing osteoclastic bone resorption, but also by decreasing osteoblastic bone formation. Due to adverse effects involving the spine, devastating fractures can occur.[56] Bone loss reportedly has occurred with prophylactic as well as therapeutic UFH doses. In addition, UFH is stored in the bone for an extended period, and its effects on

bone loss are not immediately reversible when therapy is discontinued.[3] Limited studies in humans and animals suggest that LMWHs produce less bone loss then UFH, thus lowering the risk of osteopenia. It appears that LMWHs decrease only the rate of bone formation and do not enhance osteoclastic activity leading to bone resorption.

Use of UFH in Pregnant Women

Pregnancy often results in a hypercoagulable state characterized by increased levels of coagulation factors, resistance to natural anticoagulants, reduced venous flow, and venous trauma at delivery.[57] This condition is associated with an increased risk of deep vein thrombosis and pulmonary embolism, which is a leading cause of maternal death. Long-term UFH therapy is commonly administered in at-risk, pregnant women for prevention and treatment of VTE and to prevent fetal loss in women with antiphospholipid antibodies.[3] An estimated 30% of pregnant women treated with UFH will lose at least 10% of their bone mass; 2% will experience vertebral fractures.[57] Controlled clinical trials comparing UFH with LMWHs in pregnant women are lacking. However, LMWHs are often recommended because they are convenient to administer and have a potentially lower risk of osteopenia. Like UFH, these agents do not cross the placenta.

Conclusion

Unfractionated heparin is associated with a high rate of drug-related problems because of its inherent complex pharmacology and high potential for medication errors. These drug-related problems adversely affect patient outcomes and place an additional financial burden on health care institutions. Recommendations of the Heparin Consensus Group for minimizing medication errors and drug-related problems associated with anticoagulants are provided in Appendix 1.

Today, safer alternative anticoagulation therapies such as the LMWHs are available. When compared with UFH, these alternative therapies provide equivalent or superior efficacy for numerous indications. Therapy with LMWHs decreases opportunities for errors throughout the drug therapy process, in part because of their convenient dosing and administration as well as limited monitoring requirements. In addition, these agents are associated with lower rates of drug-related problems.

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Appendix 1. Recommendations for Minimizing Medication Errors and Drug-Related Problems Associated with Anticoagulation Agents

1. A multidisciplinary medication error reporting program is recommended for all institutions, which fosters problem resolution and education.
2. Specific preventive measures for high-alert drugs such as UFH should be implemented for the reduction of medication errors.
3. All patients receiving anticoagulants must be monitored routinely for drug-related problems.