Pitfalls in the Use of Anticoagulants

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Anticoagulants are in widespread use for the management of a variety of conditions, ranging from thrombus prevention to the treatment of arterial and venous occlusion. As with any effective therapy, recognition of adverse effects is critically important for the safe use of these drugs. Pitfalls in the use of heparins include dosing in close proximity to invasive procedures; not closely monitoring patients in whom dose adjustments may be required, such as the very obese, the elderly, and patients with renal or hepatic failure; failing to make dose adjustments during pregnancy; and not recognizing when patients are developing heparin-induced thrombocytopenia or osteoporosis. Pitfalls in the use of unfractionated heparin include delays in achieving a therapeutic activated partial thromboplastin time (aPTT) and failure to consider the effects of protein binding in acutely ill patients. A pitfall in the use of low molecular weight heparin is giving prophylactic doses when therapeutic doses are indicated. Pitfalls in the use of warfarin are stopping heparin before the warfarin is fully effective; failing to maintain the International Normalized Ratio within the therapeutic range; failing to adjust the dose of warfarin because of changes in diet, renal or hepatic failure, and exposure to new drugs; failing to stop warfarin at an appropriate interval before an invasive procedure; and giving warfarin during pregnancy. Pitfalls in the use of thrombin inhibitors include using them with thrombolytic agents; giving them in proximity to invasive procedures; not adjusting the dose for renal or hepatic failure; and failing to consider the effect of these agents on the prothrombin time when initiating warfarin therapy.

(Hemodial Int., Vol. 6, 47–53, 2002)

Key words

Anticoagulants, adverse events, bleeding, thrombosis

Introduction

Anticoagulants are in widespread use for the management of a variety of conditions, ranging from thrombus prevention to the treatment of arterial and venous occlusion. As with any effective therapy, recognition of adverse effects is critically important for the safe use of these drugs. Over the years, a number of pitfalls associated with the administration of antithrombotics have come to be recognized. These include inadequate dosing, precipitation of bleeding, and thrombocytopenia. The purpose of this review was to help clinicians avoid these pitfalls. Knowledge of when and how to give anticoagulants will result in better patient outcomes. In the broadest sense, anticoagulants may be defined as agents that affect platelet function, clot formation, and clot dissolution. However, in this presentation, only pitfalls in the use of heparins, warfarin, and direct thrombin inhibitors will be examined.

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Heparins

Lack of efficacy

In the treatment of patients with venous thrombosis, it is very important that heparin be dosed aggressively during the first 24 hours. Failure to give appropriate doses is associated with thrombus extension or new thrombus formation [1]. The factors that dictate the initial dose of heparin are the patient's body weight, the extent and location of the thrombus, and concomitant disorders. Weight is taken into consideration by most heparin nomograms, such as that of Raschke *et al.* [2], which suggest an initial bolus of 80 U/kg followed by a continuous infusion of 18 U/kg/hour. Whether to modify heparin doses based on the extent and location of the thrombus is controversial; some clinicians would give larger doses for ileofemoral vein thrombosis or large pulmonary emboli. On the other hand, the intensity of heparin treatment should be decreased if there is a history of recent bleeding or recent surgery; the presence of lesions likely to bleed, such as tumors, aneurysms, or peptic ulcers; central nervous system disease; or liver or kidney failure.

Ireland *et al.* examined both subcutaneous and intravenous heparin dosing in patients on hemodialysis [3]. They concluded that giving a bolus of 5000 U followed by a continuous infusion of 1500 U/hr during dialysis completely suppressed the generation of fibrinopeptide A and prevented fibrin formation in the extracorporeal circulation.

Another important but infrequently recognized factor in heparin dosing is the acuity of patient illness. Very sick patients often have increased concentrations of heparin-binding proteins in their plasma [4]. Protein binding of heparin reduces the efficacy of the drug and results in inadequate anticoagulation, as measured by the activated partial thromboplastin time (aPTT). Failure to rapidly achieve a therapeutic aPTT is associated with an increase in thrombus recurrence. To avoid the pitfall of inadequate heparin dosing, the clinician should use a heparin nomogram, repeat aPTT measure-

ment frequently during the first 24 hours, and aggressively increase heparin doses until the aPTT is within the therapeutic range.

Heparin [unfractionated heparin (UH)] is rapidly being supplanted by low molecular weight heparin (LMWH). In addition to having much less binding to plasma proteins, LMWH's have greater bioavailability than UH when given via the subcutaneous route. This means that they may be given subcutaneously for the initial treatment of thrombosis, and usually do not require laboratory monitoring. There has been considerable uncertainty about whether monitoring is required for patients who are obese, elderly, or have renal failure. While full weight-based doses appear to be well tolerated by the obese and the elderly, a recent study suggests that the dose of LMWH should be reduced by a third for patients with a creatinine clearance of less than 30 mL/minute [5].

However, in some patients, such doses may be inadequate. For clinicians who wish to monitor LMWH therapy, a difficulty is that the available monitoring test, the anti-factor Xa assay, does not accurately reflect the range of antithrombotic activities of LMWH. However, the anti-Xa assay can be used to gauge the safety of treatment, as values in excess of 0.8 anti-Xa units can be associated with bleeding [6]. Until a better test becomes available, it would be prudent to periodically measure anti-Xa levels in patients receiving very high doses of LMWH (*i.e.*, patients weighing more than 120 kg), patients older than 75, and patients with a creatinine clearance of less than 30 mL/min. If LMWH is used for hemodialysis, a bolus dose of 175 – 200 U/kg at the beginning of dialysis prevents coagulated fibers in the dialyzer in more than 80% of dialyses [7]. Anti-Xa levels measured 4 hours into dialysis average 0.8 U/mL and rarely exceed 1 U/mL.

Similarly to UH, LMWH's may be used for prophylaxis as well as treatment of thrombosis. A pitfall is administering prophylactic doses when treatment doses are indicated. Full doses are required for the treatment of acute thrombosis. However, it is often unclear whether patients with atrial fibrillation or thrombosed vascular catheters or grafts need such doses. In general, treatment doses are given in these situations unless there is a strong risk of bleeding.

Another pitfall leading to inadequate heparin dosing is failure to adjust the dose of heparin during pregnancy in patients with treatment indications for anticoagulation (prosthetic heart valves, recent thromboembolism). With the increase in body weight and the expansion of blood volume that occur at the beginning of the third trimester, the requirements for heparin increase [8]. When UH is given, the aPTT should be measured monthly until term, and the dose of heparin increased accordingly. If LMWH is administered, the anti-Xa assay is performed 4 hours after the morning dose, and the LMWH dose adjusted to achieve an anti-Xa level of approximately 0.5 – 1.2 U/mL. Alternatively, the dose may be changed in proportion to the pregnancy weight gain [9].

Lack of safety (bleeding)

Bleeding in patients receiving UH is due to host factors as well as drug characteristics. Some host factors have been noted above; weight, age, renal and hepatic failure are each associated with an increased risk for hemorrhage [10]. Landefeld *et al.* [11] examined patient-specific factors associated with bleeding during the initiation of anticoagulant therapy. Of 82 patients with renal disease, 11 (13%) had major bleeding and 8 (10%) had minor bleeding. The role of the renal disease in enhancing the risk of bleeding is unclear. Hirsh [12] notes that the precise pathway of heparin elimination is uncertain, and that studies of the influence of renal disease on its pharmacokinetics have been inconsistent. Therefore, careful monitoring of the aPTT is essential in patients receiving heparin. Bleeding often occurs in those patients whose aPTT is persistently prolonged, that is, whose aPTT values are outside the therapeutic range for more than 24 hours. Careful monitoring of the aPTT, and downward dose adjustments of heparin as needed, may decrease the frequency of bleeding.

Another pitfall is failure to recognize major bleeding in those receiving anticoagulants. While the most frequent sites of bleeding are the gastrointestinal and genitourinary tracts (46%), wound and soft tissue (31%), and upper respiratory tract (6%), subtler bleeding occurs in the retroperitoneal space (3%) and central nervous system (2%) [13]. Retroperitoneal hemorrhages may present with only vague back or abdominal discomfort, weakness, tachycardia, and hypotension. They should be suspected in any patient treated with anticoagulants who complains of these symptoms and has an unexplained fall in hematocrit. A decline in serum sodium and a rise in serum potassium under these circumstances may be an indication of bilateral adrenal hemorrhage. Headache may be the only symptom of central nervous system bleeding. In brief, one has to be vigilant for signs and symptoms of overt or occult hemorrhage in any patient receiving heparin.

Spinal and epidural hematomas constitute another hazard of therapy with heparins. These hematomas have occurred mainly in persons injected with heparins just prior to or after epidural catheter placement. Most of these patients were elderly women undergoing orthopedic procedures, and many received concomitant dosing with ketorolac, a non-steroidal anti-inflammatory analgesic that inhibits platelet function [14]. Mammen *et al.* [15] have the following recommendations regarding the use of LMWH's:

1. That LMWH be dosed 12 hours before or 2 hours after placement of an epidural catheter
2. That medications that affect platelet function, such as aspirin or ketorolac, be avoided
3. That catheter removal be timed when the level of anticoagulant is at its lowest point (usually just prior to the next scheduled dose)
4. That clinicians should be alert to the signs and symptoms of cord compression.

The management of bleeding due to heparins depends on the severity of the hemorrhage and the temporal relationship to the heparin dose. If bleeding is life threatening or extensive, and the heparin has been given within 2 – 3 hours, reversal with protamine may be attempted [16]. One milligram of protamine is given for every 100 U of heparin infused, but this dose must be adjusted downward based on the usual half-life of heparin of 90 – 120 minutes, so that only 0.5 mg is given at 60 minutes and 0.375 mg at 120 minutes post-dose. Protamine may also be given to reverse the anticoagulant effect of LMWH, but is only about 60% effective, neutralizing mainly the anti-thrombin but not the anti-Xa activity of the LMWH. The adverse effects of protamine include hypotension and hypersensitivity reactions.

The development of heparin-induced thrombocytopenia (HIT) is another major problem in the use of heparins. A transient decline in platelet count after bolus administration is usually not of clinical concern and is termed HIT type I. However, thrombocytopenia on an autoimmune basis (HIT type II) occurring after several days' exposure or re-exposure to UH or LMWH is of great importance. In patients with thrombosis, platelets become activated and platelet factor 4, normally present only within cytoplasmic organelles, is exposed on the platelet surface. When heparin is administered, the drug, if present in appropriate (stoichiometric) concentrations, wraps around the platelet factor 4 molecules, altering their structure and rendering them antigenic. The antibodies that are formed bind to the heparin–platelet factor 4 complexes on the surface of platelets, leukocytes, and endothelial cells. The consequence is activation of these cells, resulting in thrombocytopenia, thrombus formation, and vessel occlusion [17]. Platelet counts decline to half or less of their former levels, and new thrombi appear in arteries or veins.

Warkentin [18] has recently described several paradoxes associated with HIT. First, while it is true that LMWH is less likely to provoke HIT than is UH, there is significant cross-reactivity, such that more than 90% of antibodies that react with UH will also react with LMWH. Therefore, it is contraindicated to give LMWH to patients developing HIT following treatment with UH. Second, the use of warfarin for the management of acute thromboses is contraindicated. This is because the development of HIT is associated with a profound decline in the major physiological anticoagulant, protein C. Warfarin induces a further decline in protein C levels, leading to worsening thrombosis and, particularly, venous gangrene [19]. Third, although platelet counts decline in patients with HIT, the infusion of platelets is contraindicated. Because bleeding is usually minimal, platelets are not required and, in fact, they simply aggravate thrombosis. Finally, stopping heparin does not prevent further episodes of thrombosis. The circulating anti-platelet antibodies continue to provoke clotting, which may occur days to weeks after the heparin has been discontinued. It is necessary to give therapeutic doses of another type of antithrombotic agent, such as a direct thrombin inhibitor, heparinoid (danaparoid), or pentasaccharide, to prevent further thromboses.

Other adverse consequences of administering heparins are osteoporosis, mild increases in liver enzymes, and hyperkalemia due to aldosterone antagonism. Only osteoporosis is clinically important. It affects about 30% of persons receiving daily doses of heparin for periods longer than 1 month [20]. The extent of osteoporosis appears to be less with LMWH than with UH [21]. Lai *et al.* [22] examined a variety of markers of bone formation and resorption in stable dialysis patients switched from heparin to LMWH. They observed that levels of tartrate-resistant acid phosphatase, a marker of bone resorption, were elevated when heparin was used for dialysis, but declined when LMWH was substituted. Levels increased when patients were switched back to heparin. There was also a suggestion of improvement in bone mineral density measurements during the LMWH dialyses.

Rarely, skin rashes will appear in persons allergic to pork products; changing from UH to LMWH will not help because the LMWH's are also prepared from porcine intestinal mucosa. However, pentasaccharide is entirely synthetic and the direct thrombin inhibitors are not prepared from animal material, so that either type of anticoagulant would be suitable for such patients.

Warfarin

Lack of efficacy

Warfarin is an anticoagulant with a slow onset of action; 5 days of exposure are required before levels of the vitamin K-dependent clotting factors (factors II, VII, IX, and X) have reached levels low enough that thrombosis is prevented. A major pitfall in the use of warfarin is discontinuing heparin before the warfarin has become fully effective. This error is facilitated by the use of the prothrombin time for monitoring warfarin therapy. The prothrombin time is very sensitive to the levels of factor VII; reductions in the concentration of this factor occur quickly after warfarin is instituted. Prolongation of the prothrombin time occurs before the concentrations of the other vitamin K-dependent factors are low enough to prevent thrombosis. Heparins should be continued until the International Normalized Ratio (INR; the expression of the prothrombin time) has been greater than 2.0 for at least 48 hours.

International Normalized Ratio values fluctuate with warfarin dosage, composition of diet, concurrent illnesses, exposure to various medications, and many other factors. INR levels below the therapeutic range (generally < 2.0) are accompanied by new and recurrent episodes of thrombosis. This has been documented most extensively by trials of warfarin in patients with atrial fibrillation. Hylek *et al.* [23] demonstrated that, as the INR fell below 2.0, the risk of stroke rose exponentially, with an odds ratio of 3 at an INR of 1.5, and 15 at an INR of 1.0. A variety of drugs will antagonize the effect of warfarin and lower the INR; these include anticonvulsants,

oral contraceptives, and certain anti-infectives, such as rifampin and griseofulvin. In addition, herbal products such as Saint-John's-wort induce warfarin resistance. Patients must be informed about the effects of these agents, and the INR monitored frequently so that appropriate dose adjustments can be made.

Lack of safety

Warfarin is a vitamin K antagonist; therefore, a decrease in vitamin K availability, due to either poor diet or failure to absorb the vitamin, will potentiate the effect of the warfarin and promote bleeding. A recent study observed that the highest odds ratio for coumarin-associated bleeding was the presence of diarrhea, suggesting failure of vitamin K absorption [24]. Other significant factors were fever, liver impairment, and congestive heart failure. To prevent bleeding, patients must be warned to have INR testing immediately if situations arise that alter vitamin K availability, such as nausea, vomiting, fever, and diarrhea. Other factors that increase sensitivity to warfarin are older age [25], renal failure, and a large number of medications and herbal products. The latter include antibiotics such as the cephalothins, acetaminophen (6 – 8 tablets/day), amiodarone, gingko, and ginseng. To avoid overshooting the INR when warfarin therapy is started, initial doses should not exceed 5 mg per day [26].

The kidney is not the major site of warfarin metabolism, but the association of bleeding with warfarin therapy in patients with renal failure is well established [27]. Studies performed more than 50 years ago showed that coumarin derivatives were well tolerated by some patients with renal disease [28]. However, uremic persons often have gastrointestinal lesions, such as angiodysplasia and gastritis, making them more prone to bleeding. Dosing of warfarin in hemodialysis patients is limited mainly by vitamin K availability; those patients whose nutritional status is borderline will be more sensitive to the drug, and the recovery of their prothrombin complex factors after cessation of warfarin will be more prolonged.

Recent studies note that venous thrombosis is a chronic disease: as many as 15% of patients will have a recurrence in the first 2 – 3 years after anticoagulants are discontinued [29], suggesting the need for long-term anticoagulation. The cumulative risk for bleeding with prolonged warfarin therapy (4 years) was 3% per year in low-risk patients and 53% in high-risk patients (defined as age > 65, previous gastrointestinal bleeding, history of stroke, and several other comorbid conditions) [30]. The frequency of bleeding can be decreased by anticoagulation clinics managed by persons skilled in warfarin control, and by point-of-care devices, enabling patients to monitor their own anticoagulation [31].

Situations will arise in persons on long-term anticoagulation requiring anticoagulant therapy to be temporarily discontinued. Invasive procedures usually can be safely performed when the INR is less than 1.5. Giving insufficient time for the INR to decline is a pitfall that may result in periprocedural bleeding. After warfarin is discontinued, the length of time required for the INR to decline to below 1.5 is dependent on the patient's age; in one study, it occurred in 3 days in patients under 55, and in 5 days in patients over 55 years [32]. In more than 75% of subjects, the INR was less than 1.5 by 4.7 days. Warfarin effect is readily reversed by the administration of vitamin K. If the INR is higher than 5, an oral dose of 1 – 5 mg will bring the INR back into the therapeutic range within 24 hours [33]. However, if the patient is having major bleeding or is unable to take oral medications, the vitamin K may be given either intravenously or subcutaneously. If vitamin K is given intravenously, it should be diluted in a large volume of fluid and given slowly to avoid hypersensitivity reactions. For several days after vitamin K is given via the parenteral route, there will be resistance to subsequent warfarin therapy. If the patient is actively bleeding, it will be necessary to rapidly replenish clotting factors. This can be done with fresh frozen plasma, but large volumes (1 L or more) are usually necessary. If this fluid load cannot be tolerated, concentrates of clotting factors may be infused. Recombinant activated factor VIIa is an effective but expensive replacement therapy.

Warfarin-induced gangrene was mentioned above in conjunction with heparin-induced thrombocytopenia; it was attributed to low levels of protein C. Similarly, warfarin may induce skin and muscle necrosis in patients deficient in proteins C or S, whether these deficiencies are congenital or acquired. Caution must be exercised when administering warfarin to patients that potentially may have low levels of these vitamin K-dependent anticoagulant proteins. These would include persons with a family history of thrombosis, as well as persons that might be vitamin K depleted because of poor nutrition, diarrhea, or other factors. Such individuals should not receive warfarin unless the vitamin K deficiency is remedied and they are first fully anticoagulated with heparin. The initial doses of warfarin should be 2 mg or less [24].

Teratogenicity and bleeding occur in neonates when warfarin is given during pregnancy. The greatest risk for warfarin embryopathy is between the 6th and 12th weeks [34], and there is an important risk of bleeding when the drug is given from the 32nd week to term. Thus, avoiding warfarin during pregnancy is the wisest course. Warfarin need not be stopped prior to conception, but once pregnancy is established, the drug must be discontinued. Heparin and LMWH do not cross the placenta and are therefore suitable to administer during pregnancy. Warfarin may be resumed after delivery; the amounts of warfarin in breast milk are too small to affect the neonate [35], especially if vitamin K has been given to the infant at the time of delivery.

Direct thrombin inhibitors

Agents under discussion

Hirudin is an irreversible inhibitor of thrombin. Recently, a recombinant hirudin, lepirudin, was approved by the Food and Drug Administration (FDA) for the management of HIT.

Bivalirudin is a reversible inhibitor of thrombin. It is FDA approved for the treatment of patients with unstable angina undergoing percutaneous transluminal coronary angioplasty.

Argatroban is a reversible inhibitor of thrombin. It is FDA approved for the management of HIT.

Ximelagatran is a reversible, orally active thrombin inhibitor and is in clinical trials for the treatment of venous thrombosis. It has not been approved by the FDA at the time of this writing.

Safety

All the thrombin inhibitors may cause bleeding if dosing guidelines are exceeded (Table I). Furthermore, when hirudin was administered in conjunction with thrombolytic agents in acute coronary syndrome trials, excessive bleeding was observed and the drug was withdrawn. Lepirudin is given by continuous intravenous infusion to patients with HIT. The drug is excreted by the kidney; doses must be reduced in patients with renal failure. Argatroban is also given intravenously for the treatment of HIT; however, it is metabolized by the liver. Therefore, HIT patients with renal failure are more easily managed with argatroban, and lepirudin is used in patients with liver failure. The aPTT is used to monitor both agents; it is imperative that values not exceed 2 times the control value in order to avoid bleeding. Bivalirudin is given as a continuous intravenous infusion following a loading dose, and is monitored with the activated clotting time test. Compared with heparin, bivalirudin-treated patients had fewer major hemorrhages (3.7% vs 9.3%) and required fewer transfusions (2% vs 5.7%) [36,37]. Other adverse effects, such as hypotension, nausea, and headache, were comparable to heparin.

Ximelagatran is an oral direct thrombin inhibitor. When compared with a regimen consisting of LMWH followed by warfarin, ximelagatran was found to be equally as effective in limiting the progression of venous thrombosis [38]. Major bleeding was observed in 2 of the 150 patients in each group. Larger trials are currently in progress. Ximelagatran is eliminated by the kidney. After administration of an oral dose, 13.9% was excreted by normal subjects, but only 8% by patients with renal impairment, and the half-life of the drug was twice as long [39].

Patients with HIT requiring hemodialysis pose major problems in management. There are several alternatives: dialysis without anticoagulants, regional citrate anticoagulation, or use of pharmacologic anticoagulants not associated with HIT [40]. Danaparoid and pentasaccharide (fondaparinux) are two potentially safe heparin derivatives; however, danaparoid is presently unavailable in the United States, and experience with pentasaccharide in hemodialysis is very limited. Both are monitored using the anti-Xa assay. Hemodialysis has been accomplished using argatroban and lepirudin. The aPTT may be used for monitoring and, while it appears to accurately reflect argatroban levels, it has only a fair correlation with plasma concentrations of lepirudin, especially when these are elevated (aPTT > 70 seconds). A more accurate assay method is the ecarin clotting time. Ecarin directly activates prothrombin to thrombin, a reaction inhibited by hirudin in a dose-dependent fashion. Ximelagatran prolongs the aPTT, but the relationship between the plasma concentration and the prolongation of the clotting time is non-linear [39]. Reversal of the anticoagulant effects of these agents is problematic, as there are no specific antidotes. Bleeding may be treated with recombinant factor VIIa or other clotting factor concentrates. Some, such as lepirudin, may be cleared from the circulation by hemofiltration.

A pitfall in the use of these agents is the administration of inadequate doses of warfarin when making the transition from thrombin inhibitor to warfarin. This occurs because all these agents prolong the prothrombin time. The effect on the prothrombin time is variable, depending on the sensitivity of the prothrombin time reagent and the degree of dilution of the patient sample [41]. Complicated nomograms exist for calculating the effect of the thrombin inhibitor on the prothrombin time. A simpler approach is to decrease the dose of the thrombin inhibitor by 50% on the third day of warfarin therapy. The smaller dose has less of an effect on the prothrombin time, allowing estimation of the appropriate warfarin dose. The risk of inadequate anticoagulation seems small, as the patient is receiving both drugs, albeit both are at subtherapeutic levels. To avoid the pitfall of warfarin-induced venous gangrene in patients with HIT, warfarin should not be initiated until the platelet count is clearly increasing and signs of HIT have subsided.

TABLE I FDA-approved direct thrombin inhibitors.

Agent	*Test*	*Therapeutic range*	*Dose adjustment*
Lepirudin	aPTT @ 2 hours (or ecarin[a])	1.5–2.5×control	Renal failure
Bivalirudin	ACT+ @45 minutes	300–350 sec	Renal failure
Argatroban	aPTT @ 2 hours	1.5–3.0×control	Liver failure

[a] Ecarin clotting time every 15 minutes for cardiopulmonary bypass surgery.
aPTT = activated partial thromboplastin time; ACT = activated clotting time.

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