Warfarin-Induced Skin Necrosis and Venous Limb Gangrene in the Setting of Heparin-Induced Thrombocytopenia

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Background: Heparin-induced thrombocytopenia (HIT) is a common, often catastrophic, syndrome that produces the most hypercoagulable of states. Emerging therapeutic strategies use alternative anticoagulants; warfarin’s place is being reexamined. Early in the course of warfarin therapy, there may be net procoagulant effects because of the inhibition of protein C. With HIT, it has been suggested that unopposed warfarin can precipitate venous limb gangrene. There are also reports of warfarin-induced skin necrosis. We seek to confirm and increase awareness of the risks of warfarin with HIT.

Methods: We describe 6 patients with HIT seen at 3 medical centers in whom frank or impending venous limb gangrene, central skin necrosis, or both were temporally related to warfarin initiation.

Results: At warfarin initiation, 5 patients had recognized HIT and 1 had it recognized later. Complications emerged after 2 to 7 days, and consisted of warfarin-induced skin necrosis (n=5) and venous limb gangrene (n=2); 1 patient had both. This emerged with unopposed warfarin in 4 patients and as a direct thrombin inhibitor was being withdrawn in 2. All had supratherapeutic international normalized ratios. One patient required leg and breast amputations, and another one died.

Conclusions: Because of the early effects on protein C, warfarin can precipitate venous limb gangrene and/or skin necrosis in the extreme hypercoagulable milieu of HIT. With HIT, unopposed warfarin should be avoided and caution is needed during transition from a direct thrombin inhibitor. Warfarin should be initiated at modest doses in patients with HIT after platelet recovery. Implications extend to warfarin initiation with other thrombotic diatheses.

Arch Intern Med. 2004;164:66-70

Author affiliations are given at the end of the article. Drs Rice and Bartholomew have been consultants for and on the speakers bureau of Berlex Pharmaceuticals (which markets lepirudin for heparin-induced thrombocytopenia) and GlaxoSmithKline (which markets argatroban for heparin-induced thrombocytopenia); Dr Rice has received research support (not for this study) from GlaxoSmithKline; and Drs Rice and Bartholomew have been consultants for The Medicines Company (which markets bivalirudin for percutaneous coronary intervention in patients with heparin-induced thrombocytopenia).

WARFARIN, THE STANDARD ORAL ANTICOAGULANT USED BY MILLIONS DAILY, MAY HAVE PROCOAGULANT ACTIONS IN THE FIRST DAYS OF USE BECAUSE THE VITAMIN K–DEPENDENT NATURAL ANTICOAGULANT PROTEIN C HAS A SHORTER HALF-LIFE THAN MOST γ-CARBOXYLATED PROCOAGULANTS (FACTORS II, IX, AND X). THIS HELPS EXPLAIN THE EARLY EMERGENCE OF WARFARIN-INDUCED SKIN NECROSIS, A MICROTHROMBOTIC LESION TROPIC TO CENTRAL FATTY AREAS OF THE BODY. PATIENTS WITH CONGENITAL PROTEIN C DEFICIENCY ARE PARTICULARLY SUSCEPTIBLE.1,2

Heparin-induced thrombocytopenia (HIT) is a common, often catastrophic, syndrome that produces the most hypercoagulable of states, with 30% to 75% of patients having thrombotic complications.3,4 Warfarin therapy in patients with HIT can cause progression of deep venous thrombosis to venous limb gangrene.5 Classic warfarin-induced skin necrosis has also been seen with HIT.6-10

Logically, early warfarin effects on protein C could be deleterious in the extreme hypercoagulable milieu surrounding HIT. Unopposed warfarin continues to be used pending wider appreciation of the risks. We describe 6 patients, all of whom met the established criteria for the diagnosis of HIT (decrease in platelet count by 50% at an appropriate time after heparin exposure without other likely causes). Our observations in these patients (seen in 3 medical centers over several years) confirm warfarin’s dangers and highlight specific management considerations in the transition period from direct thrombin inhibitors.

REPORT OF CASES

Summary data, including indications for heparin therapy, maximum recorded international normalized ratios (INRs), and outcomes, for all patients are given in the Table.
PATIENT 1

A 58-year-old man had traumatic vertebral fractures requiring surgery. Postoperatively, he experienced femoral vein thrombosis and pulmonary emboli. Intravenous unfractionated heparin therapy was started, with a platelet count of $441 \times 10^3/\mu L$. Warfarin, 10 mg/d, was added on day 9. Heparin was discontinued when the platelet count decreased to $120 \times 10^3/\mu L$ and to $83 \times 10^3/\mu L$ on days 10 and 11, respectively. Warfarin therapy was continued. On day 14, a necrotic ulcer appeared on the thigh (Figure, A). The prothrombin time was 21 seconds (estimated INR, 4.0); the platelet count was $133 \times 10^3/\mu L$, the fibrinogen level was normal, and fibrin split products were mildly elevated. Warfarin was discontinued, but the skin necrosis progressed and the patient died of septicemia.

PATIENT 2

After knee trauma and surgery, a 50-year-old woman had purulent material drained from her knee. Antibiotics were given via a central venous catheter flushed with unfractionated heparin. The platelet count was $318 \times 10^3/\mu L$. She was readmitted on day 8 for symptomatic venographically demonstrated thromboses in the right arm. Intravenous heparin was administered. The readmission platelet count of $109 \times 10^3/\mu L$ decreased the next day to $43 \times 10^3/\mu L$, then to a nadir of $17 \times 10^3/\mu L$. Heparin was discontinued, HIT was confirmed by an enzyme-linked immunosorbent assay, and lepirudin therapy was begun. Rapidly progressing arm cyanosis mandated alteplase for 2 days. A ventilation/perfusion scan showed a moderate probability of a pulmonary embolism. Lepirudin therapy was resumed, but the arm remained pregangrenous and the platelet count remained about $100 \times 10^3/\mu L$. Warfarin therapy was started at 5.0 mg/d on day 23, and increased to 7.5 mg/d on day 25. On day 26, lepirudin was discontinued (INR, 3.1). A painful 10-cm black lesion with surrounding ecchymoses appeared on the left breast on day 28. The INR was 4.5, and the platelet count was $87 \times 10^3/\mu L$. Warfarin was discontinued, vitamin K was administered, and lepirudin therapy was resumed. The breast improved over several days, as the platelet count increased to $240 \times 10^3/\mu L$. Low-dose warfarin, 2.5 mg/d, was re instituted and lepirudin was eventually discontinued. Protein C and S levels were normal.

PATIENT 3

A 55-year-old man underwent coronary artery bypass surgery and received intravenous heparin for 3 days postoperatively for atrial fibrillation. The platelet count on hospital discharge (day 7) was $224 \times 10^3/\mu L$, but was $47 \times 10^3/\mu L$ on readmission 4 days later, with right leg deep vein thrombosis. Enzyme-linked immunosorbent and serotonin release assays confirmed HIT, and lepirudin therapy was initiated. Warfarin, 21 mg, was given for the next 3 days. On day 9, the INR was 2.7, the platelet count was $45 \times 10^3/\mu L$, and lepirudin was discontinued. The leg worsened. Lepirudin therapy was restarted with warfarin. On day 13, the INR was 3.3 and warfarin therapy was continued alone. Thrombocytopenia persisted. On day 14, worsening cyanosis of the leg gave the appearance of impending venous limb gangrene. The INR was 5.8. Lepirudin therapy was resumed, warfarin was discontinued, and vitamin K was administered. Signs of gangrene resolved over 2 days, as the platelet count increased to normal. The patient was discharged to continue taking danaparoid sodium.
PATIENT 4

A 53-year-old woman was treated with intravenous heparin for a pulmonary embolism. Warfarin, 10 mg/d, was added on day 3. The platelet count decreased to $247 \times 10^3/\mu L$ at baseline to $83 \times 10^3/\mu L$ on day 5, the INR was 6.1, and painful purpuric lesions of both calves appeared, progressing to full-thickness necrosis. HIT was diagnosed based on clinical variables and a positive enzyme-linked immunosorbent assay result. Heparin and warfarin were discontinued, as vitamin K, fresh frozen plasma, and danaparoid were given. The patient required grafts to both legs. Recurrent pulmonary emboli were believed to be due to cross reactivity of antibodies with danaparoid (dose, 1500 U subcutaneously twice a day; the result of serotonin release for cross reactivity was positive). Argatroban therapy was substituted. Warfarin was reintroduced at 1 mg/d, and escalated slowly, overlapping with argatroban for 15 days. A hypercoagulability evaluation revealed only an elevated anti–cardiolipin IgG level (without a lupus anticoagulant).

PATIENT 5

A 24-year-old woman with systemic lupus erythematosus received intravenous heparin for a pulmonary embolism. Warfarin, 10 mg/d, was added on day 3. The platelet count decreased from $247 \times 10^3/\mu L$ at baseline to $83 \times 10^3/\mu L$ on day 5, the INR was 6.1, and painful purpuric lesions of both calves appeared, progressing to full-thickness necrosis. HIT was diagnosed based on clinical variables and a positive enzyme-linked immunosorbent assay result. Heparin and warfarin were discontinued, as vitamin K, fresh frozen plasma, and danaparoid were given. The patient required grafts to both legs. Recurrent pulmonary emboli were believed to be due to cross reactivity of antibodies with danaparoid (dose, 1500 U subcutaneously twice a day; the result of serotonin release for cross reactivity was positive). Argatroban therapy was substituted. Warfarin was reintroduced at 1 mg/d, and escalated slowly, overlapping with argatroban for 15 days. A hypercoagulability evaluation revealed only an elevated anti–cardiolipin IgG level (without a lupus anticoagulant).

PATIENT 6

A 72-year-old woman received alteplase and heparin for an acute myocardial infarction. The platelet count was $190 \times 10^3/\mu L$. She underwent coronary artery bypass grafting several days later. Warfarin was given for postoperative atrial fibrillation. Four days postoperatively, she developed pain and discoloration of the left breast, right leg, and left foot (Figure, C). The INR was 6.4 and the platelet count was $68 \times 10^3/\mu L$. The breast and venous leg lesions rapidly progressed. She required a mastectomy and a below-the-knee amputation, and eventually a left transmetatarsal amputation. Five weeks later, she was readmitted with upper extremity swelling. Ultrasonography confirmed axillary-subclavian and femoral venous thromboses. The platelet count decreased from $126 \times 10^3/\mu L$ to $26 \times 10^3/\mu L$ after 3 days of intravenous heparin therapy. Subcutaneous enoxaparin sodium therapy produced the following acute systemic reaction: flushing, tachycardia, and tachypnea. An inferior vena cava filter was placed, and argatroban was given for 2 weeks. A hypercoagulability profile showed anti–cardiolipin antibodies and a low protein S level.

COMMENT

Warkentin et al described the syndrome of venous limb gangrene complicating HIT and related it to warfarin use. Compared with unaffected patients, those with venous limb gangrene had higher prothrombin INRs, lower protein C activities, and persistently elevated thrombin-antithrombin complexes. This syndrome caused more limb amputations with HIT than did arterial thromboses. It occurred in 12% of patients with HIT and venous thrombosis given warfarin (with or without ancrod). Like

our patient 6, one patient with gangrene also developed classic central skin necrosis. Other case reports document warfarin-induced skin necrosis complicating HIT. The warfarin-induced skin necrosis with HIT seems clinically identical to the classically described syndrome in terms of onset in the first days of warfarin use and predilection for fatty areas of the body. As in patients with other thrombogenic diatheses in whom frequently more than one hypercoagulable state coexists, it is not surprising that some of our patients had additional thrombogenic risk factors (patients 5 and 6). Our series confirms the dangers of venous limb gangrene and skin necrosis when initiating warfarin therapy in patients with HIT.

Our patients illustrate a gamut of HIT clinical scenarios. In patients 1, 4, and 5, heparin was discontinued for acute HIT, then unopposed warfarin was initiated or continued. In patient 6, HIT was initially unrecognized. We emphasize that the emergence of warfarin-induced skin necrosis or worsening venous thrombosis should alert to the possibility of underlying HIT; patient 6 could have been spared further morbid and life-threatening complications. In patients 2 and 3, there was some delay-onset component to the HIT, and both had warfarin-related complications emerge during overlap with lepirudin therapy. To our knowledge, we are the first to report that in patients with HIT, the transition period from a direct thrombin inhibitor to warfarin can be potentially dangerous. Others have begun to recognize warfarin-induced worsening of venous thromboses in patients with HIT during the transition from the direct thrombin inhibitor lepirudin or argatroban. Argatroban has significant effects on prothrombin INR, which introduces challenges with warfarin overlap (as noted on the package insert), yet this is a double-edged sword, with risks not only of anticoagulation overshoot with bleeding but also of warfarin-related prothrombotic effects if the argatroban is discontinued (or even held) prematurely. While lepirudin has less effect on the prothrombin INR, recent exhortations to reduce doses to minimally therapeutic levels during warfarin transition may raise similar dangers.

In the extreme prothrombotic milieu of HIT, alternative anticoagulants should be administered. Most patients will require transition to warfarin for the indication that first mandated anticoagulation, for thromboses that arose secondary to HIT, or for protection from the extreme risk of new thrombosis in isolated HIT. Several precautions could minimize the risks of warfarin initiation in patients with HIT, including (1) first waiting for the platelet count to increase to near normal as the HIT is “cooled”; (2) initiating modest doses, avoiding an overshoot of the target INR; and (3) shunning unopposed warfarin and assuring adequate levels of an alternative anticoagulant during transition. Wallis et al observed no increase in thrombotic events with warfarin treatment in 51 patients with HIT, 16 with HIT-related thromboses. Warfarin doses were modest (mean, 3.5 mg); therapy was started several days before HIT in many patients or a mean of 3 days after HIT in half the patients, when the platelet count was generally $100 \times 10^9/\mu L$. In all our patients, as in prior reports, thrombotic complications correlated with supratherapeutic prothrombin INRs.

Beyond implications toward the recognition and management of HIT, our observations bear generally on the optimal initiation of warfarin therapy. It is increasingly clear that protein C inhibition before effective paralysis of procoagulant pathways is more than a theoretic concern. In fact, early warfarin exacerbation of thrombotic diatheses has been reported with hereditary protein C deficiency, with cancer-related disseminated intravascular coagulation, and now confirmed with HIT. While there may be low-risk situations in which warfarin can be initiated unopposed, prudence dictates adequate systemic anticoagulation before warfarin use in any active thrombotic process. In a warfarin-naive patient, we endorse initial doses of 5 mg/d, sometimes lower in situations such as HIT.

Accepted for publication January 24, 2003.

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This study was presented in part at the American Society of Hematology 43rd Annual Meeting; December 2, 2001; Orlando, Fla.

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