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 This emerged with unopposed warfarin in 4 patients and as a direct thrombin inhibitor was being withdrawn in 2.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.

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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 $441 \times 10^3/\mu\text{L}$. Warfarin, 10 mg/d, was added on day 9. Heparin was discontinued when the platelet count decreased to $120 \times 10^3/\mu\text{L}$ and to $83 \times 10^3/\mu\text{L}$ 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 120 $10^3/\mu\text{L}$ and to a nadir of $83 \times 10^3/\mu\text{L}$. Warfarin was discontinued, vitamin K was administered. Signs of gangrene were noted. The INR was 4.5, and the platelet count was 87 $10^3/\mu\text{L}$. Lepirudin therapy was resumed, warfarin was discontinued, vitamin K was administered, and lepirudin therapy was resumed. The breast improved over several days, as the platelet count increased to $240 \times 10^3/\mu\text{L}$. Low-dose warfarin, 2.5 mg/d, was re instituted and lepirudin was eventually discontinued. Protein C and S levels were normal.

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 $318 \times 10^3/\mu\text{L}$. She was readmitted on day 8 for symptomatic venographically demonstrated thromboses in the right arm. Intravenous heparin was administered. The readmission platelet count of $109 \times 10^3/\mu\text{L}$ decreased the next day to $43 \times 10^3/\mu\text{L}$, then to a nadir of $17 \times 10^3/\mu\text{L}$. 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 $100 \times 10^3/\mu\text{L}$. 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 $87 \times 10^3/\mu\text{L}$. Warfarin was discontinued, vitamin K was administered, and lepirudin therapy was resumed. The breast improved over several days, as the platelet count increased to $240 \times 10^3/\mu\text{L}$. Low-dose warfarin, 2.5 mg/d, was re instituted and lepirudin was eventually discontinued. Protein C and S levels were normal.
PATIENT 4

A 53-year-old woman was treated with intravenous heparin for a pulmonary embolism. Warfarin, 10 mg/d, was begun. The platelet count decreased to 86 × 10^3/µL on day 7, the INR was 3.2, and heparin was discontinued. The result of an enzyme-linked immunosorbent assay for heparin-induced antibodies was positive. Three days later, violaceous discoloration of both breasts developed and progressed to full-thickness skin necrosis (Figure, B). Warfarin was discontinued, and lepirudin therapy was instituted as the platelet count reached a nadir of 22 × 10^3/µL. Extensive surgical debridement of both breasts was performed. Warfarin therapy was later rescheduled at 1 mg/d, and increased gradually until the INR was therapeutic; then, lepirudin was discontinued. The patient had normal protein C and S levels and negative hypercoagulability panel results.

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 × 10^3/µL at baseline to 83 × 10^3/µL 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 × 10^3/µL. 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 × 10^3/µL. 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 × 10^3/µL to 26 × 10^3/µL 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 al5 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 ancred). 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 cli-
nically identical to the classically described syndrome in
terms of onset in the first days of warfarin use and pre-
dilection for fatty areas of the body. As in patients with
other thrombotic 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 dan-
gers of venous limb gangrene and skin necrosis when ini-
tiating warfarin therapy in patients with HIT.

Our patients illustrate a gamut of HIT clinical sce-
narios. 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 morbidity and life-threatening compli-
cations. In patients 2 and 3, there was some delayed-
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 poten-
tially dangerous. Others have begun to recognize war-
farin-induced worsening of venous thromboses in pa-

tients with HIT during the transition from the direct
thrombin inhibitor lepirudin or argatroban. Argatroban
has significant effects on prothrombin INR, which in-

troduces 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 prothrom-

bin INR, recent exhortations to reduce doses to mini-
mally therapeutic levels during warfarin transition may
raise similar dangers.

In the extreme prothrombotic milieu of HIT, alter-
native anticoagulants should be administered. Most
patients will require transition to warfarin for the indica-
tion that first mandated anticoagulation, for thromboses
that arose secondary to HIT, or for protection from the ex-

treme risk of new thrombosis in isolated HIT. Several
precautions could minimize the risks of warfarin ini-
tiation 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 over-
shoot of the target INR; and (3) shunning unopposed war-
farin and assuring adequate levels of an alternative anti-

shooting of the target INR; and (3) shunning unopposed war-
farin-related complications before effective pa-

ralysis of procoagulant pathways is more than a theo-

retic 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 war-
farin can be initiated unopposed, prudence dictates ade-
quate systemic anticoagulation before warfarin use in
any active thrombotic process. In a warfarin-naïve pa-


tient, we endorse initial doses of 5 mg/d, sometimes lower
in situations such as HIT.

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