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Venous Limb Gangrene During Overlapping Therapy With Warfarin and a Direct Thrombin Inhibitor for Immune Heparin-Induced Thrombocytopenia

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We report two patients with deep-vein thrombosis complicating immune heparin-induced thrombocytopenia who developed venous limb gangrene during overlapping therapy with a direct thrombin inhibitor (lepirudin or argatroban) and warfarin. In both patients, therapy with the direct thrombin inhibitor was interrupted during persisting severe athrombocytopenia while warfarin administration continued. Both patients exhibited the typical feature of a supratherapeutic international normalized ratio (INRs, 5.9 and 7.3) that has been linked previously with warfarin-associated venous limb gangrene. These data suggest that warfarin anticoagulation be postponed in patients with acute heparin-induced thrombocytopenia until substantial recovery of the platelet count has occurred. Am. J. Hematol. 71:50–52, 2002.

Key words: heparin-induced thrombocytopenia; deep-vein thrombosis; warfarin; venous limb gangrene; direct thrombin inhibitor

INTRODUCTION

Venous limb gangrene is a devastating syndrome of limb necrosis associated with coumarin (warfarin) therapy of deep-vein thrombosis (DVT) complicating immune heparin-induced thrombocytopenia (HIT) [1–4]. Affected patients have a typical clinical profile. First, progression to necrosis occurs in a limb with active DVT despite palpable or Doppler-identifiable pedal pulses. Second, gangrene typically occurs only after HIT has been diagnosed, heparin discontinued, and warfarin commenced or continued. And third, patients usually have an INR above the therapeutic range [1–4]. Previous studies indicate this syndrome is associated with a profound disturbance in procoagulant–anticoagulant balance during treatment of HIT-associated DVT: hypercoagulability (thrombin generation) persists despite warfarin therapy, while the supratherapeutic INR is a surrogate marker of severe protein C depletion during warfarin use [1–5]. Recently, a similar syndrome of limb gangrene complicating cancer-associated hypercoagulability and DVT was linked to warfarin therapy [6].

Direct thrombin inhibitors (DTIs) can be used to treat HIT-associated thrombosis. In the U.S., lepirudin (recombinant hirudin) and argatroban (small-molecule DTI) became available in 1998 and 2000, respectively [7]. While reviewing our experience with DTI therapy at William Beaumont Hospital, we became aware of two patients who developed venous limb gangrene during overlapping therapy with DTIs and warfarin.

PATIENTS AND METHODS

Medical and laboratory records were reviewed for 39 consecutive patients treated with a DTI over an 18-month

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TABLE I. Summary of Clinical Course

	Patient 1 (82-year-old male)	Patient 2 (62-year-old female)
Clinical setting	UFH "flushes"	Post-coronary artery bypass grafting
HIT antibodies	Positive by EIA	Positive by EIA
HIT-associated thrombosi(e)s	Left popliteal vein to external iliac vein; right ileofemoral DVT	Left common femoral DVT
Platelet counts		
Baseline	271	246
At starting DTI	25	50
At stopping DTI	46	19
Platelet count nadir	17 (2 days before starting DTI)	15 (4 days after starting DTI)
DTI therapy (hr) prior to onset of gangrene	Lepirudin × 131 hr; stopped for ~53 hr; then resumed × 9 hr[a]	Argatroban × 18 hr
Reason(s) for stopping DTI	INR = 5.9 on DTI and warfarin after 7 days of warfarin treatment (see doses below)	High INR (4.1) on DTI plus warfarin and fall in platelet count on DTI (from 50 to 17)
Warfarin dosing prior to gangrene (mg/day)	5, 2, 1, 2, 1, 7.5[b], 4[b] given on seven consecutive days (warfarin begun on 2nd day of DTI therapy)	5,5 given on two consecutive days
Highest INR during onset of gangrene		
DTI plus warfarin	5.9	7.3[c]
After stopping DTI	3.1 (24 hr after)	2.1 (36 hr after)
Days until platelet count rose > 150 × 10^9/L	>45	12
Hypercoagulability work-up	Normal levels for protein C, protein S, antithrombin; factor V Leiden not present	Factor V Leiden and prothrombin gene mutations not present; other data NA
Management of limb gangrene and ultimate clinical course	IVC filter, lepirudin resumed, bilateral below-knee amputations; incidental finding of right-sided adrenal hemorrhage on later CT scan (possible HIT-associated adrenal necrosis)	Fasciotomies, femoral vein thrombectomy, DTIs resumed (argatroban, then lepirudin); warfarin resumed after platelet recovery; ultimately, no limb loss

[a]Lepirudin stopped after 4.5 days of overlap with warfarin when INR therapeutic, but reinstated postoperatively because the INR at surgery was 1.9.
[b]Postoperatively, higher doses of warfarin were given (7.5 and 4 mg), which led to INR rise to 5.9 (lepirudin plus warfarin) that remained elevated (3.1) 24 hr after stopping lepirudin, and was associated with progression of DVTs to limb gangrene.
[c]INR rose to 7.3 after two 5-mg doses of warfarin.

period ending June 2001. Venous limb gangrene was diagnosed when a patient had radiologically confirmed DVT that progressed to limb necrosis despite palpable or Doppler-identifiable pulses [1]. We reviewed timing and dosing of DTI and warfarin therapy in relation to platelet counts, international normalized ratio (INR), and activated partial thromboplastin time (aPTT) results. HIT antibodies were detected in the two patients with venous gangrene using an enzyme-immunoassay (GTI-PF4; GTI, Inc., Brookfield, WI) [8].

CLINICAL COURSE

Patient No. 1

An 82-year-old man developed HIT while receiving small doses of unfractionated heparin (UFH) to "flush" a percutaneously inserted central catheter used to treat postoperative wound infection. The patient developed HIT-associated bilateral lower limb DVT (Table I). Lepirudin was given in therapeutic doses (increase in aPTT from baseline of 26.5 sec to median of 55 sec during treatment). Warfarin was commenced on day 2 of lepirudin therapy. Lepirudin was discontinued after 131 hr as the INR was therapeutic at 2.6 after 4½ days of overlap with warfarin; at this time the platelet count was 51 × 10^9/L. Two days later the patient underwent incarcerated hernia repair. Lepirudin was re-initiated on that day as the INR was 1.9. Lepirudin was stopped 9 hr later because the INR rose to 5.9, and the aPTT was >100 sec. The warfarin doses on the two preceding days were 7.5 mg and 4 mg, respectively. Over the next 48 hr, lower limb ischemia progressed to bilateral limb gangrene, ultimately requiring below-knee amputations.

Patient No. 2

A 62-year-old woman developed DVT 7 days after cardiac surgery. Upon receiving UFH therapy with overlapping warfarin (5 mg on two consecutive days), the platelet count fell abruptly from 240 × 10^9/L to 50 × 10^9/L over 48 hr. HIT was diagnosed, argatroban (0.5 μg/kg/min) was substituted for UFH. The aPTT rose on argatroban from 31.9 (baseline) to 59 sec. However, the argatroban was stopped after only 18 hr, for two reasons: the platelet count fell from 50 to 19, and the INR rose to 4.1. During the ensuing 24 hr after argatroban was stopped, the limb with DVT developed distal necrosis; at

this time, the INR rose to 7.3 (Table I). The patient had distal tissue sloughing but did not require amputation.

DISCUSSION

We describe two patients who developed venous limb gangrene during overlapping therapy for HIT-associated DVT with a DTI (lepirudin or argatroban) and warfarin. In both patients, DTI therapy was interrupted during persisting thrombocytopenia. In both patients, the INR was supratherapeutic (5.9 and 7.3) shortly before onset of limb gangrene, and limb necrosis occurred despite palpable pedal pulses. These clinical features suggest progressive microvascular thrombosis secondary to acquired natural anticoagulant depletion during warfarin therapy of HIT-associated hypercoagulability [1–6]. Previous studies indicate that the supratherapeutic INR is a surrogate marker for protein C depletion via parallel reduction in factor VII [1–6]. Unfortunately, plasma samples were not available to permit testing of thrombin generation or vitamin K-dependent factors.

These cases suggest that warfarin therapy should be avoided during acute HIT managed with a DTI. If for any reason DTI therapy is interrupted during persisting thrombocytopenia, abrupt recurrence of HIT-associated hypercoagulability, together with warfarin-induced natural anticoagulant failure, has the potential to lead to progression of DVT to venous gangrene. By postponing warfarin until substantial resolution of thrombocytopenia has occurred, this complication may be preventable.

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