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Reinstituting Warfarin in Patients Who Develop Warfarin Skin Necrosis

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Skin necrosis is a rare but serious complication of oral anticoagulation with coumarin derivatives. Frequently, the necrosis can be extensive and may result in major morbidity and mortality. The majority of these patients require prolonged anticoagulation for life-threatening conditions such as deep venous thrombosis and pulmonary embolism. Resuming oral anticoagulants in the face of skin necrosis is a difficult decision for both the patient and the physician. Because long-term heparin therapy is inconvenient and is associated with significant side effects, we reviewed the literature to find alternative treatment strategies. A *Medline search* was done, and all papers published in English since 1967 were reviewed. Of 58 cases with skin necrosis attributed to oral anticoagulants, oral anticoagulation was resumed in 7 patients with no resulting adverse effects. Warfarin is the most widely used coumarin derivative in the United States. Based on our review, we make recommendations for resuming warfarin in patients who have developed skin necrosis when the clinical condition absolutely requires prolonged anticoagulation.

Key words: warfarin skin necrosis, anticoagulation, alternative strategies

BACKGROUND INFORMATION

Skin necrosis due to coumarin derivatives was first reported in 1954. It is estimated that 0.001–0.7% of patients treated with coumarin congeners develop this condition, which characteristically affects females between the third and tenth day of treatment. A prominent clinical feature is its marked predilection for anatomic regions abundant in subcutaneous fat, such as breasts, abdomen, buttocks, and thighs [1]. Initially, the skin lesions are characterized by pain and erythema followed by edema and petechial hemorrhages that rapidly progress to frank necrosis. Frequently, the injury extends into the subcutaneous fat and, after a variable period, simulates the eschar of a full-thickness burn. Usually, debridement and skin grafting are required for complete healing. On occasion, severe involvement of a breast or penis has resulted in amputation.

Skin necrosis from coumarin derivatives occurs more often in patients being treated for deep venous thrombosis than in patients treated for cardiac conditions and arterial occlusive disease [1]. This finding suggests that both deep venous thrombosis and oral anticoagulant-induced skin necrosis may reflect an underlying hypercoagulable state. Deficiencies of protein C, protein S, and antithrombin III are among the hypercoagulable conditions that may predispose to skin necrosis. Recent reports indicate that approximately fifty percent of the cases of coumarin skin necrosis are associated with protein C deficiency. Screening for the recently described entity of hereditary protein C resistance may increase the relevance of this association [2]. It is hypothesized that initiation of oral anticoagulation leads to a rapid decline in protein C, triggering small vessel thrombosis and necrosis before the anticoagulated state is fully established. This theory is supported by the known short half-life (5 hr) of protein C, a vitamin K-dependent factor, and by the presence of thrombi in the postcapillary venules, thought to be the underlying pathologic mechanism leading to necrosis. Most patients who develop skin necrosis have conditions requiring prolonged and, in some instances, indefinite anticoagulation. Resuming oral anticoagulants after developing skin necrosis can be a difficult decision for both the patient and

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TABLE I. Reinstituting Oral Anticoagulants Following Oral Anticoagulant-Induced Skin Necrosis

#	Sex	Age	Drug used	Site of necrosis	Underlying disorder	Treatment resumed	Follow-up duration	Investigators/ year
1	F	58	Sodium warfarin	Anterior left thigh	Unknown	Sodium warfarin started at a low dose; 5 mg/day	Unknown	Bahadir et al. [4]/1977
2	F	47	Warfarin	Right side of abdomen	Monoclonal gammopathy	Warfarin resumed without a loading dose	Unknown	Jones and Cunningham [5]/1979
3	F	23	Phenprocoumon	1st, 2nd, and 3rd toes of left foot	Protein C deficiency	Phenoprocoumon started at a lower dose (3 mg/day); no loading dose used	3 mo	Pabinger et al. [6]/1986
4	M	53	Warfarin	Right flank and buttock	Unknown	Dose of warfarin decreased from 10 mg to 7.5 mg	2 mo	Horn et al. [7]/1981
5	M	17	Acenocoumarol fluindione	Lower limbs	Protein C deficiency	Phenprocoumon given at 1 mg/day in divided doses on day 1; 1.5 mg/day for 4 days and 3 mg/day thereafter	3 mo	Samama et al. [8]/1984
6	M	61	Coumarin	Penis	Protein C deficiency	Coumarin started without a loading dose; heparin overlapping	3 mo	Barkley et al. [9]/1989
7	F	21	Nicoumalone	Thigh	Protein S deficiency	Dose of nicoumalone decreased to maintain a British ratio of 2.0	5 yr	Craig et al. [10]/1990

the physician. While some patients are candidates for vena caval plication procedures, the only satisfactory alternative form of anticoagulation is with low-molecular-weight heparin, for which the long-term complications have not been established. Moreover, this form of therapy requires daily injections and is considerably more expensive than oral anticoagulant therapy [3]. Because of these considerations, we performed a Medline search for cases of oral anticoagulant-induced skin necrosis published in English since 1967.

RESULTS

Of the 58 cases we reviewed, oral anticoagulation was resumed in 7 patients [4–10]. The clinical characteristics of the seven patients are summarized in Table I. Four of the patients were females and three were males. Ages ranged from 17 to 61 years. The drugs responsible for necrosis were sodium warfarin, phenprocoumon, acenocoumaral, fluindione, coumarin, and nicoumalone. The initial necrosis was seen from day 1 to day 5 but was seen most frequently on day 4. Three patients had protein C deficiency, and one had protein S deficiency. In the other three patients, an underlying cause of hypercoagulability was not identified. Prothrombin times ranged from 19.0 to >50 sec at the time of development of necrosis.

After a decision to resume oral anticoagulation was made, the anticoagulant was administered at a lower dose. A loading dose was not administered. Heparin anticoagulation was started before oral anticoagulation was reinstituted and was continued until therapeutic anticoagulation with the oral agent was achieved. Four of the seven patients were treated with this approach with no recurrence of necrosis. Patient #4 was on 7.5 mg of warfarin to maintain anticoagulation. He developed thrombophlebitis while on 7.5 mg of warfarin, and the dose was increased to 10.0 mg/day. This regimen resulted in skin necrosis, which necessitated withdrawal of warfarin. The patient was treated with heparin, and warfarin was resumed at 7.5 mg, without a loading dose; no further evidence of thrombosis or necrosis was seen.

Patient #5 had ileofemoral thrombosis at age 17, treated initially with intravenous heparin followed by subcutaneous heparin. Three attempts at oral anticoagulation, two with acenocoumarol and one with fluindione, resulted in ecchymosis and bruises, and therapy had to be discontinued. The fourth attempt was made with an initial dose of phenprocoumon, 1 mg, while the patient was heparinized. Doses were gradually escalated, and a therapeutic prothrombin time was obtained after 10 days without recurrence of skin necrosis. Heparin was then discontinued.

Patient #7 developed skin necrosis when treated with

nicoumalone with the INR at 4.7. The dose of nicoumalone was decreased to maintain the INR at 2.0 with no recurrence of necrosis. In five of the seven patients, follow-up duration (2 months to 5 years) was reported during which there were no complications.

CONCLUSIONS

Skin necrosis as a result of treatment with coumarin and its derivatives can result in major complications requiring prolonged hospitalization, skin grafting, secondary infection, amputation, and death. From our review, we believe that treatment can be resumed with oral anticoagulants when long-term anticoagulation is absolutely essential. A loading dose should not be used. Anticoagulation should be started with intravenous heparin. This should be followed by oral anticoagulation with a small to moderate dose of the oral agent (e.g., warfarin 2–5 mg/day). After achieving full therapeutic anticoagulation (INR >2.0) with the oral agent, heparin should be stopped.

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