Warfarin Necrosis

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Skin and subcutaneous tissue necrosis is a rare complication of warfarin therapy. Although the incidence is low, with increased use of warfarin family physicians need to be aware of this potentially catastrophic event. This article reviews the history of warfarin necrosis and discusses its clinical presentation. The histologic findings with necrosed lesions are described, with emphasis on the possible pathogenesis of this disorder. Treatment options based on existing clinical experience as outlined in the literature are discussed. *(Arch Fam Med. 1992;1:105-108)*

Warfarin sodium is an anticoagulant derived from the parent compound coumarin and is the most common oral anticoagulant used in the United States.[1] It is commonly used for thromboembolic prophylaxis of pulmonary emboli and deep venous thrombosis, after cardiac valve replacement, and after certain orthopedic operations. It is also increasingly being used in patients with atrial fibrillation because of the increased incidence of thromboembolic events with this condition.[2] The common complications of warfarin, which are related to bleeding from hypocoagulability, are well known to family physicians. One of the rarer complications of coumarin derivatives is necrosis of skin and subcutaneous tissues. Though well documented in the literature, warfarin-induced necrosis may not be readily recognized. Skin and subcutaneous tissue necrosis have been associated with all coumarin derivatives.[3] Although it is recognized that the parent compound coumarin has no anticoagulant properties, in this article, the terms *warfarin necrosis* and *coumarin necrosis* are used synonymously.[4]

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HISTORY

In 1943, Flood et al[5] reported a case of necrosis of the breast attributed to thrombophlebitis migrans disseminata. This patient was taking a coumarin-derived anticoagulant, but the association was not fully recognized at the time. Approximately 10 years later, in Europe, Verhagan[6] recognized the association with coumarin necrosis and published descriptions of 13 cases in 1954. Coumarin necrosis was first reported in the English-language literature in 1961, when Kipen[7] described gangrene of the breast as a complication of oral anticoagulant therapy. Nalbandian and colleagues[8] reported three cases of warfarin-induced necrosis in 1965. Nalbandian reviewed the literature and found that, of 87 reported cases at that time, all but five were in European journals.[8] In 1988, Cole and colleagues[9] estimated that approximately 200 cases of coumarin-induced necrosis had been reported. By 1990, Comp et al[10] reported more than 300 articles dealing with oral anticoagulant-induced skin necrosis.

CLINICAL PRESENTATION

The reported incidence of coumarin necrosis is estimated to be 0.01% to 0.1% of all patients who have received oral anti-

coagulants.[11] Although warfarin necrosis has been described in all age groups and in both sexes, the typical patient is an obese, middle-aged woman. Ages have ranged from 16 to 93 years, with the median age being 54 years, and with 75% of all cases having occurred in women.[3,9,10,12] The necrosis has a predilection for the lower half of the body, mostly in areas of abundant subcutaneous tissue, such as the thighs and buttocks.[3] However, the breast is a relatively common site of involvement, and necrosis of the penis has been reported seven times.[3,13-18] The necrosis does not usually involve the fascia or muscular tissues, but involvement of the muscle layer has been reported.[19] Warfarin necrosis usually appears between the third to and fifth day of therapy, although it may appear up to the 10th day.[3,12] There is an isolated report of late-onset warfarin necrosis (occurring 18 months after initiation of warfarin therapy) in a patient with infectious mononucleosis.[20]

Although warfarin necrosis has occurred in patients receiving heparin, most of the early cases were associated with large initial doses of oral anticoagulant or the use of oral anticoagulants alone.[13-16,18,21] Necrosis may go unrecognized and can be confused with other medical conditions such as pyoderma gangrenosum or cryofibrinogenemia.[10] It may also mimic skin and subcutaneous hemorrhage caused by overcoagulation with heparin or heparin-induced necrosis of the skin and subcutaneous tissue.[22] This distinction is critical because of differences in proper treatment.

The initial symptom of warfarin necrosis is pain in the involved area accompanied by an erythematous flush, which is apparently poorly demarcated.[3] Petechial hemorrhages appear next, followed by red, blue, and/or black discoloration.[3] These lesions then become necrotic and may be accompanied by hemorrhagic blisters.[3,9,21] **Figure 1** shows a patient with warfarin necrosis. The involved sites may require débridement and possibly skin grafting. They may also heal spontaneously with or without scarring.[9,16,17] Death has been associated with warfarin necrosis, but usually as a complication of the underlying medical disorder.[7] The clinical entity of warfarin necrosis is distinct from warfarin-related purple toes syndrome. Purple toes syndrome is a complication of warfarin therapy involving thrombosis of digits, mainly the toes, and is caused by cholesterol microemboli.[23] It occurs 3 to 8 weeks after initiation of warfarin therapy and is unrelated to warfarin necrosis. The histologic findings with warfarin-necrosed tissue are remarkable for thrombosis of the small veins, precapillary venules, and capillaries.[14,19] The arteries are usually spared.[11,14] The thrombus contains large amounts of fibrin and demonstrates perivascular infiltration with leukocytes and histiocytes.[10,14,23]

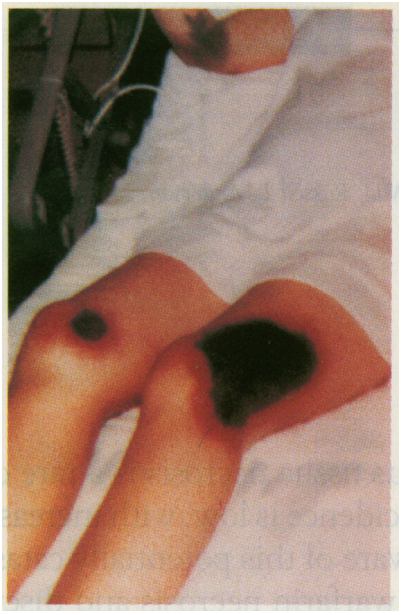

Figure 1. *A patient with warfarin necrosis. The involved sites may require débridement and skin grafting.*

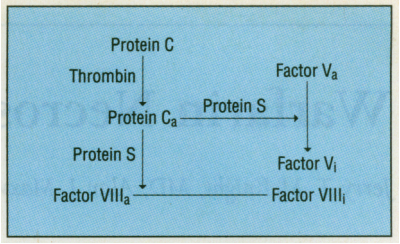

Figure 2. *A simplified version of the interaction of proteins C and S with activated (a) and inactivated (i) clotting factors V and VIII.*

PATHOGENESIS

Several theories have been proposed to explain the phenomenon of warfarin necrosis. Some believe coumarin congeners have direct toxic effects while others believe warfarin necrosis is a hypersensitivity reaction.[8,9] The most widely held theory proposes that this phenomenon is related to transient hypercoagulability.[9,10,12,17] This is substantiated by the association between warfarin necrosis and other hypercoagulable states, such as deficiency of protein C, deficiency of protein S, presence of the lupus anticoagulant, and antithrombin III deficiency.[24-29]

Protein C and protein S are vitamin K–dependent factors that inhibit coagulation.[30-34] Protein C is a vitamin K–dependent glycoprotein that is activated by a thrombin-thrombomodulin complex to form protein C_a, the activated form of protein C.[30] Thrombomodulin is a receptor protein on the surface of endothelial cells that binds thrombin and greatly increases the rate at which protein C is activated.[30,31] Activated protein C inactivates factors V and VIII, thus limiting the clotting process.[30,31,34] Deficiencies in protein C have been associated with recurrent thromboembolic disease.[35-37] Protein S is a vitamin K–dependent plasma protein that inhibits the clotting of blood by serving as a cofactor for activated protein C.[33] **Figure 2** depicts the interaction of protein C and protein S with factors V and VIII. **Figure 3** shows the coagulation cascade in a simplified diagram. Deficiency of protein S has been associated with recurrent thromboembolism and warfarin necrosis.[38] A proposed mechanism for warfarin necrosis involves a relative deficiency of protein C early in the course of warfarin therapy.[24,26,39,40] Protein C antigen and protein C activity

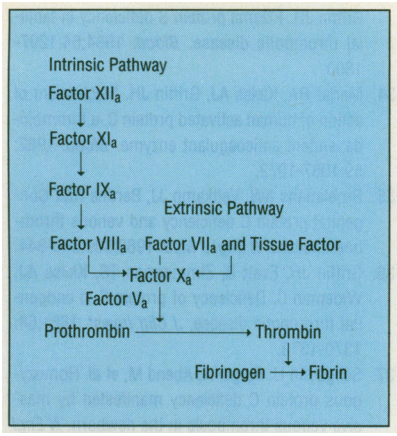

Figure 3. *A simplified version of the coagulation cascade. Activated factors are indicated by the letter a.*

decreases rapidly early in the course of treatment because of the short half-life of protein C (8 hours), thus causing an imbalance between protein C and clotting factors IX (half-life of 24 hours) and X (half-life of 48 hours).[24,26,30,39,41,42] (Other vitamin K–dependent coagulation factors and their half-lives are as follows: factor II, 2 to 5 days; factor VII, 1.5 to 6 hours; and protein S, 42 hours.[30,41]) This is a reason not to give large initial doses of warfarin (>15 mg). With the commonly used factor VII–dependent prothrombin time it is possible for a patient to have a therapeutic prothrombin time and, concomitantly, be hypercoagulable because of a relative protein C deficiency and nearly normal levels of factors IX and X.

The lupus anticoagulant is one of a group of immunoglobulins present in patients with rheumatologic diseases that has been associated with coumarin necrosis.[28] The lupus anticoagulant interferes with the phospholipid-dependent biochemical mechanisms of coagulation and causes a condition known as the antiphospholipid syndrome.[28,32] Coumarin necrosis has also been associated with antithrombin III deficiency.[29] Many cases of warfarin necrosis are not explainable by protein C deficiency, protein S deficiency, antithrombin III deficiency, or the antiphospholipid syndrome. Thus, further research and elucidation of this condition is needed.

TREATMENT

Some reports[6,8] indicate that continuation of oral anticoagulants has little effect on the progression of necrosis once it has begun. However, it seems prudent to discontinue warfarin as the initial step once the diagnosis is recognized.[12] Reports in the literature[9,16,20,43] have advocated giving vitamin K, but this has not been shown to affect outcome. Full heparinization should be continued or resumed and surgical consultation should be obtained because approximately 50% of the patients will require surgical débridement.[9,43] Administration of fresh frozen plasma has been used to prevent the recurrence of warfarin necrosis associated with protein C deficiency and may be helpful in treating this condition.[40] Fresh frozen plasma quickly replaces vitamin K–dependent clotting factors, including protein C, that are depleted by warfarin.[44] Fresh frozen plasma should be given and full heparinization should be performed once the diagnosis has been established.[40] Allowing the necrotic area to demarcate before surgical débridement has been advocated because tissue that initially appears necrotic may heal with varying degrees of scarring.[17]

Patients have been successfully restarted on warfarin after an episode of warfarin necrosis.[17,40,45] This was achieved using small initial doses of warfarin sodium concomitant with full heparinization.[40,45] Simultaneous administration of fresh frozen plasma was given for the first 2 days in a reported case.[40] The negative medicolegal aspects of resuming warfarin therapy in patients who had experienced a previous episode of necrosis must be considered and hematologic consultation is advisable. The alternative in treating patients requiring long-term anticoagulation because of thromboembolic disease is subcutaneous administration of heparin. This has the obvious drawback of inconvenience, and, more importantly, the risk of osteoporosis associated with long-term heparin use.[46]

When treating deep venous thrombosis and pulmonary emboli, full heparinization should be achieved before initiation of warfarin therapy, and there should be an overlap of 5 to 6 days before discontinuing heparin.[47] This overlap will help prevent a transient hypercoagulable state caused by normal levels of factors IX and X and depression of protein C that occurs early in the course of warfarin therapy. Although use of a shorter course of heparin has been suggested for cost savings, a shorter course may not always be appropriate for this reason.[48]

SUMMARY

Family physicians need to be aware of this unusual but potentially catastrophic complication associated with warfarin use. Prompt recognition could limit damage and, although the pathogenic mechanisms are not fully known, methods of prevention and treatment have been recommended. Warfarin should not be given in a loading dose (> 15 mg), and full heparinization should be achieved before the initiation of warfarin therapy when treating deep venous thrombosis and pulmonary emboli. In treating patients with histories of warfarin necrosis, low doses of warfarin should be used initially with a longer overlap of heparin. In this setting, consideration should be given for the use of fresh frozen plasma during the first few days of warfarin therapy. This regimen should also be used for anyone having known or suspected protein C deficiency, protein S deficiency, or any other hypercoagulable syndrome. Once warfarin necrosis is diagnosed, warfarin should be discontinued and full heparinization continued or resumed. Fresh frozen plasma should be given, although it has not been proven that this will limit tissue damage.

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Figure 1 is courtesy of Craig S. Kitchens, MD, Gainesville, Fla.

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