

lation syndrome.² Although its occurrence is uncommon, recognition of the association is important. I agree that warfarin should be avoided during pregnancy. Low-molecular-weight heparin preparations do not cross the placenta, but levels of antifactor Xa should be monitored when such agents are used during pregnancy. Recommendations that focus on anticoagulation in pregnancy are offered by the American College of Chest Physicians.³

Castiglione notes the potential for detrimental prothrombotic effects with the use of low-dose warfarin in elective joint replacement. Hypercoagulability may result because the anticoagulant protein C has a half-life similar to that of factor VII (6 to 8 hours). Without the use of concomitant heparin or low-molecular-weight heparin, warfarin may decrease protein C levels before factors II and X reach desired levels, resulting in a transient prothrombotic state.⁴ This is of most concern in patients with established thrombosis and those at high risk. Evidence-based recommendations strongly support the use of low-molecular-weight heparin in joint replacement (grade 1A).⁵ The use of warfarin to achieve a target international normalized ratio of 2.0 to 3.0 is also recommended (grade 1A), rather than the use of "low-dose warfarin." Adherence to current recommendations would appear to be prudent. Newer oral anticoagulants that include antithrombin and anti-factor Xa inhibitors may soon replace this drug.

Naina and Quevedo remind us that subcuta-

neous standard heparin can be used to treat acute venous thromboembolism. They cite a randomized trial with compelling data, although that trial took a number of years to recruit patients. Substantially more data (and specific advantages) support the use of low-molecular-weight heparin, as compared with standard heparin by the subcutaneous route. The criteria for prophylaxis in the medically ill are clearly outlined in reports of clinical trials.⁵ One must consider risk factors and then individualize treatment for affected patients, realizing that venous thromboembolism may have devastating consequences and that prophylaxis is generally safe.⁵

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Imatinib as a Possible Cause of Severe Rhabdomyolysis

TO THE EDITOR: Imatinib mesylate (Gleevec [Glivec], Novartis), a protein kinase inhibitor of c-kit receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor α (PDGFR- α), is widely used for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors. Its common side effects (diarrhea, edema, asthenia, myalgia, and skin reactions) are most often mild and manageable.¹

We describe the case of a 25-year-old woman who received imatinib mesylate (at a daily dose of 400 mg) in a clinical trial for the treatment of aggressive fibromatosis (desmoid tumors) not

amenable to surgery.² Shortly after the initiation of treatment with imatinib, she had myalgia of growing intensity and was subsequently admitted with an extensive mucocutaneous rash, pruritus, hypereosinophilia, and an elevated level of serum creatine kinase (1068 IU per liter; upper limit of the normal range, 110).

Myocardial infarction, stroke, and other medications were ruled out as causes of the elevated creatine kinase level. Common causes of rhabdomyolysis were also ruled out. A myopathic pattern was seen on electromyography. Although the patient declined to undergo muscle biopsy, there was

no evidence of an underlying metabolic muscle disorder or myopathy. After the discontinuation of imatinib, the myalgia disappeared, and the creatine kinase level returned to normal (119 IU per liter) within a week.

After the patient provided written informed consent, imatinib was reintroduced under medical surveillance. Twenty-four hours after she received the first daily dose of 100 mg, severe myalgia reappeared and was accompanied by increased levels of the skeletal-muscle subtype of creatine kinase (1444 IU per liter) and aldolase and the presence of myoglobinuria. Again, imatinib was discontinued, and the myalgia disappeared in 3 days. The patient's desmoid tumors continued to grow and were treated with radiotherapy. As of January 2008, the patient had not reported any recurrence of symptoms of rhabdomyolysis.

Rhabdomyolysis is characterized by leakage of myoglobin and other intracellular proteins and electrolytes into the circulation, as a result of acute muscle necrosis. The latter may be due to direct muscle injury, infection, metabolic myopathy, or various toxic or pharmacologic agents, including antipsychotic drugs, colchicine, zidovudine, and statins.³ The rate of death from rhabdomyolysis is about 8%, as a result of acute renal failure, disseminated intravascular coagulopathy, or severe electrolyte abnormalities leading to cardiac dysrhythmias.³

We considered our patient's rhabdomyolysis to be induced by imatinib because of the temporal

relationship (the rhabdomyolysis occurred within a few days after the initiation of imatinib therapy), the recurrence of rhabdomyolysis with the reintroduction of the drug, and normalization of the creatine kinase level after discontinuation of the drug. Although there is extensive clinical experience with the safe use of imatinib, this observation suggests that the drug may cause severe rhabdomyolysis in a small proportion of patients.

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