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LETTER TO THE EDITOR

Recognizing Increased Sensitivity to Warfarin in Liver Dysfunction Secondary to Congestive Heart Failure

Sir,

Factors that are known to be associated with an enhanced anticoagulant response to warfarin include old age, liver diseases, and hyperthyroidism.[1] As illustrated by the case described here, patients may also become increasingly sensitive to warfarin as a consequence of worsening liver dysfunction secondary to congestive heart failure.

A 31-year-old man with recurrent pulmonary thromboembolism presented to our hospital again 10 weeks after he was put on warfarin. His main complaints were increased dyspnoea for 4 days and skin 'rash' over both legs for 1 month. He also had a 2-year history of post-concussion epilepsy which was treated by another hospital with phenytoin 200 mg daily. Pre-treatment liver function tests were normal. In the 12 months prior to the current admission, he experienced three episodes of bilateral leg pain/swelling and/or chest pain with haemoptysis. During this period, he noticed a gradual worsening of his exertional dyspnoea. He was first seen in our hospital during the third attack of leg pain/swelling and chest pain 11 weeks earlier. He was then found to have hepatomegaly with abnormal liver function tests (plasma alkaline phosphatase 208 U/l, normal 40–136, plasma albumin 28 g/l, normal 36–48), gross ascites, bilateral leg oedema, pulmonary hypertension with right ventricular hypertrophy and severe tricuspid regurgitation, and protein C deficiency. A diagnosis of deep vein thrombosis and pulmonary embolism was confirmed by venogram and perfusion lung scan. His international normalized ratio (INR) before anticoagulation was 1.1. He was treated with intravenous heparin infusion (days 1 to 10) and oral warfarin (10 mg on day 5, 3 mg on days 7 to 9, and 3.5 mg on day 10). On day 11, when his INR was 2.3, he was discharged home on warfarin 3 mg daily, fursemide 40 mg daily, 'slow-K' (potassium chloride 600 mg) two tablets twice daily and phenytoin 200 mg daily. He was subsequently seen in the clinic on days 21 and 50. His INR was 2.5 on day 21, and he was continued on the same medications. However, on day 50, his INR was >6.0. He was told to stop warfarin for 2 days and then reduce the dosage to 2.5 mg daily.

On the present admission, he was fully alert and orientated. His blood pressure was 130/70 mmHg and pulse rate 84 beats/min. Right ventricular heave and loud S_2 were present, suggesting pulmonary hypertension. There were fine crepitations over the lower zones of the lungs. Abdominal examination showed an enlarged liver and gross ascites. Both lower limbs were markedly swollen. Patches of skin infarction, which are a known feature of protein C deficiency, and ecchymoses were seen over the shins. His INR was >6.0 on admission, but was 2.9 after warfarin withdrawal and infusion of 4 units of fresh frozen plasma. Other abnormal laboratory findings included a reduced platelet count of 127×10^9/l (normal 140–380), a reduced plasma albumin of 32 g/l, but a raised plasma total bilirubin of 63 μmol/l (normal 0–15), alkaline phosphatase of 137 U/l (normal 40–136), and alanine aminotransferase of 235 U/l (normal 0–58). The thrombocytopenia might be due to hypersplenism accompanying spleen congestion and chronic liver disease. In view of an elevated serum level of 93 μmol/l (normal 40–79), the dosage of phenytoin was reduced to 100 mg daily. The marked diuresis of up to 4.8 l daily while he was on oral fursemide 20–40 mg daily, suggested he probably had not taken the diuretic regularly prior to admission. When he was discharged home 3 weeks later, his body weight had decreased from 65.2 to 63.4 kg. His INR had been stable at 2.0–2.5 for almost 1 week while he was on warfarin 1 mg daily. His other medications were phenytoin 100 mg daily, furosemide 40 mg daily, 'slow-K' two tablets twice and essential one tablet three times daily.

In the next 12 months, he was hospitalized three times because of congestive heart failure. Captopril 25 mg three times daily, isosorbide mononitrate 20 mg twice daily and digoxin 125 μg daily were

added. His warfarin requirements varied between 1.0–1.5 mg daily. Because of the further worsening of his heart failure and liver congestion after 17 months of anticoagulation, he became even more sensitive to warfarin, with an INR of 3.9 while he was on 0.75 mg daily. Warfarin was then stopped. He died from severe pulmonary hypertension and congestive heart failure about 18 months after the first admission to our hospital.

In general, liver diseases are associated with an enhanced anticoagulant response to warfarin. It appears that this increased sensitivity is due more to impaired hepatic synthesis of vitamin-K dependent clotting factors than to reduced rate of warfarin metabolism.[1] Studies in patients with acute viral hepatitis showed that there was an increased anticoagulant response in 20% of the subjects, without any apparent change in warfarin pharmacokinetics.[2]

Liver enzymes like transaminases and glutamyltransferase may be increased in patients treated with phenytoin, although chronic liver toxicity is quite rare after treatment with this drug.[3] The natural course in this patient would suggest that the worsening of his right heart failure was the most likely cause of the progressive liver dysfunction. His initial warfarin requirement (3 mg) was therefore smaller than the average Chinese man of his age and weight (4 mg).[4] Because of the worsening heart failure and liver dysfunction, his warfarin requirement had dropped to 1.0–1.5 mg daily within 7 weeks. However, such changes in his cardiac and liver conditions had been overlooked. Consequently, his warfarin dose was only reduced from 3 to 2.5 mg daily on day 50, and his INR remained at >6.0. His increasing sensitivity to warfarin was only realized during his second admission to our hospital.

In all patients receiving long-term warfarin, it is most important that their dose requirements are regularly and carefully reviewed taking into consideration any changes in patients' underlying medical conditions such as heart failure and liver dysfunction.

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