

# Medicinal mishap

## Fenofibrate–warfarin interaction

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### Case

A 65-year-old woman taking warfarin was admitted to hospital because she had melaena and an INR greater than 10. She also had a painful left ankle due to a large atraumatic haemarthrosis which had left her unable to weight bear. The patient had a history of type 2 diabetes mellitus complicated by chronic renal failure, peripheral vascular disease, hypertension, dyslipidaemia and hypothyroidism.

She had been treated with warfarin for 16 years for two indications, paroxysmal atrial fibrillation and a mitral valve xenograft, and her INR was usually stable. Her dyslipidaemia was managed with simvastatin, but four weeks before admission she was changed to fenofibrate. This was because she had mixed dyslipidaemia with predominant hypertriglyceridaemia. She was found to have normocytic normochromic anaemia and acute-on-chronic renal failure (estimated glomerular filtration rate of 17 mL/min).

Initial management included correction of coagulation factor deficiency with fresh frozen plasma, daily INR monitoring and withdrawal of warfarin for three days. The gastrointestinal bleeding was managed with a proton pump inhibitor given parenterally and transfusions of packed red blood cells.

While in hospital, she developed paroxysmal atrial fibrillation with rapid ventricular response rate and myocardial damage as evidenced by a small rise in troponin I. She was discharged after seven days with an INR of 2.8, in rate-controlled atrial fibrillation, and with no evidence of ongoing gastrointestinal blood loss. She was also able to weight bear.

### Comment

The patient's presentation was probably caused by the interaction between fenofibrate and warfarin. Fenofibrate is a fibric acid derivative that is approved as an adjunct to diet in the treatment of dyslipidaemia when hypertriglyceridaemia is the predominant abnormality.

There are two possible explanations why fenofibrate can amplify the anticoagulant effect of warfarin. Fenofibrate is highly protein bound *in vivo* and so has the potential to displace warfarin from its binding protein and lead to an enhanced hypoprothrombinaemic effect. In addition, fenofibrate is a mild to moderate inhibitor of CYP2C9, which is the major enzyme system responsible for warfarin metabolism.<sup>1</sup>

The product information warns that anticoagulant doses should be reduced to prevent bleeding complications. Frequent monitoring is recommended when starting treatment with fenofibrate until the INR is stabilised.

Most clinicians do not suggest a pre-emptive change in warfarin dose, although some authors recommend an empiric 20% reduction in warfarin dose when fenofibrate is initiated.<sup>1</sup> The INR should be checked 48–72 hours after the first dose of fenofibrate.

### Conclusion

Clinicians need to be aware of a potential interaction between fenofibrate and warfarin. Whenever starting fenofibrate for patients receiving concurrent warfarin, the INR should be checked 48–72 hours as the warfarin dose may need to be reduced.

### Reference

1. Kim KY, Mancano MA. Fenofibrate potentiates warfarin effects. *Ann Pharmacother* 2003;37:212-5.



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