

Letters to the Editor

Fatal phenytoin warfarin interaction

Sir,

The interaction between phenytoin and warfarin is unpredictable and poorly understood.¹ In this report we describe a fatal reaction when phenytoin was added to long standing warfarin therapy.

A 74 year old man had a right occipital infarction in November 1987 and a right frontal infarction in April 1989. In view of the recurrent strokes and embolic focus in the right carotid he was commenced on warfarin in May 1989. He was eventually discharged from hospital on 6 mg/day of warfarin with an International Normalised Ratio (INR) of 2.36 (therapeutic range 2.5–4.0). No other medications were introduced and the warfarin dose was controlled to give a ratio between 2 and 3.

He was readmitted 5 months later having had 3 generalized tonic/clonic seizures. A cerebral computed tomographic (CT) scan showed no change from before and phenytoin was started with a loading dose of 300 mg intravenously; he was maintained on 300 mg/day. His hepatic and renal function were normal. The admission INR was 2.87 and he was continued on 6 mg warfarin/day.

Seven days after admission he suddenly became pale and hypotensive after a generalized tonic/clonic seizure. He had abdominal tenderness attributed to a spontaneous retroperitoneal haemorrhage, which was confirmed by an abdominal CT scan. The INR was 10.41 and phenytoin level 10 mg/l (therapeutic range 10–20). No other drugs had been introduced. He was resuscitated

with fresh frozen plasma and intravenous fluids. His general condition improved, only to deteriorate again 3 days later, complicated by cardiac arrest from which he did not recover despite cardiopulmonary resuscitation.

Phenytoin may decrease or increase the anticoagulant effect of warfarin. A decrease has been attributed to hepatic enzyme induction,¹ and an increase to displacement of warfarin from protein binding sites.^{2,3} Also, phenytoin itself may prolong the prothrombin time.^{4,5} Because the interaction developed after several days, we believe the potentiation of warfarin effect in our patient was most likely due to displacement of warfarin from protein binding sites.

The interactions between phenytoin and warfarin are therefore complex and it is impossible to predict the effect of the interaction in each patient. On the basis of our experience, we emphasize the extreme potential for danger arising from this combination of drugs and we suggest the effects of both drugs be monitored closely when used together.

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