CASE REPORT

Warfarin sensitivity: be aware of genetic influence

TAYYABA KHAN, FARHAD KAMALI, ANN DALY, BARRY KING, HILARY A. WYNNE

Departments of Pharmacological Sciences and 1Geriatric Medicine, University of Newcastle upon Tyne, Newcastle Upon Tyne NE1 4LP, UK

Address correspondence to: H. A. Wynne. Fax: (+44) 191 222 5638. Email: H.A.Wynne@ncl.ac.uk

Abstract

Background: avoidance of over anticoagulation in response to warfarin therapy would reduce risk of associated bleeding.

Subjects: two elderly patients with venous thromboembolism exhibited extreme anticoagulant response to warfarin. Both were noted to have variant CYP2C9 alleles, which reduce the metabolic capacity of cytochrome P450 2C9.

Discussion: adverse outcomes with warfarin therapy could be explained and possibly avoided by identifying patients with variant alleles for CYP2C9 before initiation of therapy.

Keywords: anticoagulation, warfarin, cytochrome P450 2C9, genetic polymorphism

Introduction

Two patients with venous thromboembolism were significantly over anticoagulated in response to warfarin therapy at standard doses. Neither patient had any abnormality of the biochemical tests of liver function used in clinical practice, nor were they co-prescribed any drugs known to inhibit warfarin metabolism. Both had mutations of the gene coding for the CYP2C9 enzyme responsible for the metabolism of S-warfarin enantiomer.

Case reports

Case 1

An 88-year-old woman, weighing 46 kg, presented with left sided pleuritic chest pain and shortness of breath. Ventilation perfusion scan demonstrated a large mismatched perfusion defect, supporting a diagnosis of pulmonary embolism. Her baseline prothrombin time was normal. She was anticoagulated with 10 mg warfarin; her INR peaked at 9.2 on day 6, returning to below 2 by day 11, following two separate doses of 2 mg vitamin K intravenously.

Genotyping revealed her to be homozygous for the CYP 2C9*3 mutation of the gene.

Case 2

An 85-year-old woman, weighing 51 kg, presented with her right leg swollen to her groin. Doppler ultrasound indicated an extensive ileofemoral vein thrombosis extending proximally to the inguinal ligament. Her baseline prothrombin time was normal. Following 10 mg of warfarin on day 0 and 5 mg on day 1, her INR peaked at 13.2 on day 4, returning to below 2 on day 8, following two separate doses of 0.5 mg vitamin K intravenously.

Genotyping revealed her to be heterozygous for the CYP 2C9*2 mutation.

The time course of anticoagulation response to warfarin and vitamin K administration for these patients is shown in Figure 1.

Discussion

A number of factors contributed to the marked anticoagulant response to warfarin exhibited by these patients. First, sensitivity increases with age, with a 21% fall in warfarin requirements over a 15-year period [1]. Second, there is a small, but significant correlation between body weight and warfarin requirements [2], and both these patients were lightweight. Body weight is an indirect marker of liver volume, which correlates with lean
body mass. Age and liver volume together account for approximately 34% of the variation in warfarin dosage requirements [3].

Warfarin is a racemic mixture of R- and S-enantiomers with the S-enantiomer being approximately three times as potent as the R-enantiomer [4]. S-warfarin is hydroxylated by the cytochrome (CYP) 2C9 enzyme. Mutations in the CYP2C9 gene result in the expression of three allelic variants, CYP2C9*1, CYP2C9*2 and CYP2C9*3. Both CYP2C9*2 and CYP2C9*3 variants exhibit altered catalytic activity relative to CYP2C9*1, the wild type enzyme. The CYP 2C9*2 gene, expressed in vitro, demonstrates 12% of the wild type protein activity [5], whilst the CYP 2C9*3 gene, expressed in vitro, demonstrates 5% activity [6]. A correlation between CYP 2C9 genotype and warfarin sensitivity has been noted, with individuals requiring low dose warfarin (1.5 mg or less) being six times more likely to be positive for one or more variant alleles compared with the general population [6].

The elderly with CYP2C9 gene mutations, for whom warfarin sensitivity is compounded by age, are at risk of over anticoagulation during the induction period and can demonstrate a large change in INR in response to a small dose of warfarin.

Clinicians should be aware of the cumulative effects of advanced age, reduced liver volume and CYP 2C9 polymorphisms upon response to warfarin.

Key points
- Genotype investigation of two patients who exhibited extreme anticoagulant response to warfarin established that each had mutations of the gene encoding for cytochrome P450 2C9.
- The elderly with these mutations, for whom warfarin sensitivity is compounded by age, are at risk of over anticoagulation during the induction period and can demonstrate a large change in INR in response to a small dose of warfarin.

References

Received 26 March 2002; accepted in revised form 9 October 2002