CASE REPORT

The impact of genetics on the management of patients on warfarin awaiting surgery

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Abstract

Two older patients with atrial fibrillation, receiving warfarin for thromboembolic prophylaxis, with a target range of 2.0–3.0, were significantly over anticoagulated prior to elective intervention, in spite of having adhered to the standard protocol of 5 days of warfarin interruption. Neither patient had any abnormality of liver function nor was taking any interacting drug known to inhibit warfarin metabolism or affect sensitivity to warfarin. Both had variant cytochrome P2C9 (CYP2C9) alleles which reduce the metabolic capacity of the CYP2C9 enzyme responsible for the metabolism of the S-warfarin enantiomer. Need for preoperative administration of vitamin K or postponement of an operation because of an INR >1.5 could be explained by variant alleles for CYP2C9 and age.

Keywords: anticoagulation, warfarin, pharmacogenetics, older people

Case reports

A 78-year-old man weighing 87 kg, taking warfarin 13 mg per week (2 mg Monday—Saturday, 1 mg Sunday), verapamil, losartan and atorvastatin, attended urology outpatients department because of macroscopic haematuria. His venous INR was 4.4. Computed tomography scan identified a renal cyst and warfarin was discontinued to allow biopsy. Six days later, when the patient attended for renal biopsy, his INR was 4.3, despite him confirming compliance with 5 days of warfarin withdrawal as advised in the standard protocol of warfarin interruption [1]. When he returned for biopsy after a further 12 days without warfarin, his INR was 1.1. Genotyping revealed him to have heterozygous mutations (*2*3) for the CYP2C9 gene.

A 71-year-old man, weighing 86 kg, taking warfarin 14 mg per week (2 mg daily), bisoprolol, ramipril and simvastatin, was admitted 1 day before planned ureteric stone extraction. His INR at the monitoring clinic 3 weeks previously had been 2.7 and on admission was 1.8. He confirmed that he had taken his last dose of warfarin 4 days previously in accordance with the protocol given at the preoperative assessment clinic. He was given 1 mg vitamin K intravenously. The following morning INR was 1.4. Genotyping revealed him to have heterozygous mutations (*2*3) for the CYP2C9 gene.

Discussion

Warfarin is a racemic mixture of R- and S-enantiomers with the S-enantiomer being approximately three times as potent as the R-enantiomer [2]. S-warfarin is hydroxylated by the CYP2C9 enzyme to its inactive metabolite. Mutations in the CYP2C9 gene result in the expression of two allelic variants, 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 CYP2C9*2 variant enzyme demonstrates 12% of the wild-type protein activity [3], while the CYP2C9*3 variant enzyme demonstrates 5% activity [4]. Individuals with a gene mutation are more sensitive to the anticoagulant effect of warfarin and need lower doses than those without a mutation [4].
For patients on chronic therapy with warfarin awaiting elective surgery, guidelines suggest that warfarin should be stopped 5 days before the event to minimise the risk of bleeding [1], although the data upon which the guidelines are based are largely derived from methodologically weak observational studies. While this ensures that INR averages 1.24 (95% CI 1.19–1.29) after a 5-day warfarin interruption [5], some patients, 7% in one study [6], have an INR >1.5 on the day of planned surgery. Many hospitals admit anticoagulated patients on the day before elective surgery to check their INR and administer vitamin K if needed, to avoid surgery being postponed. This adds costs and risks a potentially wasted operation slot if the INR is >1.5 on the day of surgery in spite of vitamin K.

CYP2C9 variants are associated with over-anticoagulation during the induction period [7], and their pharmacokinetic influence upon decline in INR after stopping warfarin can be predicted, due to the increase in warfarin’s expected elimination half-life of 36–42 h, such that a normalisation of the INR, after interruption of warfarin, is more than the expected 5 days [8]. As the decay of the anticoagulant effect is further delayed in older patients as metabolism declines with age [9] due to reduction of liver size, the standard 5-day interruption period may not be sufficient to allow normalisation of the INR for older people with CYP2C9 gene mutations. Further research to establish the extent of any genetic- and age-related contribution to INR decay in patients stopping warfarin would clarify whether developing a pharmacogenetic-based personalised algorithm to predict the time required for INR to decline to <1.5 could obviate the need for INR checking on the day before an invasive procedure.

Key points
- In spite of 5 days of warfarin withdrawal, some patients remain too anticoagulated for surgery.
- Age and mutations of the cytochrome P2C9 gene slow metabolism of warfarin.
- An age- and pharmacogenetic-based algorithm has the potential to predict the appropriate warfarin withdrawal period for patients.

Conflicts of interest
None declared.

References

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