

AN INTERACTION BETWEEN WARFARIN AND COX-2 INHIBITORS: TWO CASE STUDIES

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In this article, the authors describe two case studies that draw attention to an interaction between warfarin and cyclo-oxygenase-2 selective inhibitors with potentially serious consequences

The risk of haemorrhagic episodes in patients receiving warfarin in combination with conventional non-steroidal anti-inflammatory drugs (NSAIDs) is well recognised, and frequently results in therapeutic dilemmas in patients with painful arthropathies who also require anticoagulation. Many prescribers consider cyclo-oxygenase-2 (COX-2) selective inhibitors to be safer than conventional NSAIDs in patients receiving warfarin and this has led to an increase in their use in these patients.

We report two previously well controlled patients taking warfarin who experienced significant rises in international normalised ratio (INR) shortly after starting a COX-2 inhibitor. Both cases (see Panels) will be reported under the yellow card scheme.

COMMENT

Warfarin is a racemic mixture of *R*-warfarin and *S*-warfarin, which differ in potency and metabolic pathways.¹ *R*-Warfarin is a less potent anticoagulant than is *S*-warfarin,¹ which is metabolised by CYP 2C9.² CYP 1A2 and CYP 3A are the enzymes responsible for the metabolism of the less potent *R*-warfarin.

There have been reported instances of significant rises in INR in patients taking rofecoxib and warfarin. Rofecoxib is known to produce inhibition of CYP 1A2,³ an enzyme involved in the metabolism of *R*-warfarin, but this mechanism seems unlikely to explain fully such a sharp change in INR since *R*-warfarin has less anticoagulant activity than *S*-warfarin.

There have also been isolated reports of an increase in INR and bleeding episodes in patients taking warfarin in combination with celecoxib. However, although celecoxib is an inhibitor of CYP 2D6,⁴ it is not known to inhibit any of the enzyme subsets that are responsible for warfarin metabolism. The possible mechanism for COX-2 inhibitors interacting with warfarin is therefore unclear.

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Case study 1: warfarin and rofecoxib

A 63-year-old man had been taking warfarin continuously for the previous five years following a second proximal deep vein thrombosis. His warfarin dose had been 3.5mg daily, which had not altered for the past nine months. His INR results in the anticoagulant clinic during this time had varied from 2.3 to 2.6. His target INR was 2.5.

He had also been taking diclofenac SR 100mg daily for rheumatoid arthritis for the previous two years, which had caused him some dyspepsia. His anti-inflammatory medication was changed to rofecoxib 12.5mg daily, which he had been taking for two weeks prior to his clinic appointment. At the clinic his INR was 7.7 and, apart from starting rofecoxib, nothing else had changed with respect to his medication or lifestyle. He was advised to stop taking warfarin for the next three days, then to restart at a lower dose (2.5mg daily). He was also advised to stop taking the rofecoxib, and to return to his general practitioner to discuss further management of his arthritis. When he attended the anticoagulant clinic one week later, his INR had fallen to 3.2 and his GP had restarted him on diclofenac.

Case study 2: warfarin and celecoxib

A 65-year-old woman had been taking warfarin for six months after being diagnosed with atrial fibrillation (target INR 2.5). She had also been taking digoxin 125µg daily from that time. At her last three anticoagulant clinic appointments, her INR had been 2.3, 2.7 and 2.2, and her dose (4mg daily) remained unchanged during this time. Three weeks before her recent clinic appointment, she had been started on celecoxib 200mg daily for osteoarthritis of the lower spine.

At clinic, her INR was 5.8. She was advised to discontinue the celecoxib and to return to her doctor to discuss future management of her osteoarthritis. She was also advised to stop taking warfarin for two days and to resume at a lower dose (3mg daily) until her next clinic appointment one week later.

Although neither of these patients experienced haemorrhagic events while taking warfarin and a COX-2 inhibitor, they were at high risk of this occurring. It was fortuitous that the patients presented in clinic when they did, so that corrective action could be taken.

The Summary of Product Characteristics for both Vioxx and Celebrex advise close

monitoring of INR in patients stabilised on anticoagulant therapy when a COX-2 inhibitor is initiated or the dose is changed.^{3,4} We recommend that all patients receiving warfarin who are co-prescribed a COX-2 inhibitor should have their INR monitored at least weekly over the first three weeks of concurrent use to ascertain whether they are susceptible to this interaction.

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