

Possible Enhancement of the Effect of Warfarin Secondary to Oral Prednisone Therapy

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INTRODUCTION

A large number of medications have been reported to either increase or decrease the effect of warfarin on the international normalized ratio (INR).¹ Therefore, knowledge of medications that may interact with warfarin is essential to ensure safe and effective use of this drug. Patients taking warfarin should undergo more frequent testing of INR upon introduction of new medications that may interact with warfarin.

In a recent systematic review of medications and foods that may interact with warfarin, oral corticosteroids were not listed as having clinically significant interactions.¹ In fact, interactions between methylprednisolone and warfarin were described as “highly improbable”.¹

We report here a clinically significant increase in INR associated with the initiation of oral prednisone therapy in a patient whose condition had previously been stabilized with warfarin therapy.*

CASE REPORT

A 45-year-old woman started oral contraceptive therapy in 2002 for irregular menstrual periods. Symptomatic distal deep vein thrombosis of the left leg was diagnosed in February 2006. The contraceptive was discontinued, and warfarin therapy was initiated and then discontinued after 6 months. Four months later, recurrent proximal deep vein thrombosis occurred in the other leg. Warfarin was restarted with the intention of being continued indefinitely.

On May 7, 2007, the patient underwent abdominal hysterectomy and bilateral salpingoophorectomy for management of abnormal uterine bleeding. She received

a prophylactic (preoperative) dose of cefazolin 1 g IV and was treated postoperatively with heparin and warfarin until discharge on May 10, 2007. She presented to the emergency department 2 days later (May 12) with a bilateral nonpruritic petechial rash distal to her knees. She was discharged the same day with a prescription for cephalexin 500 mg PO q6h for presumed cellulitis. The rash worsened over the next 3 days, and the patient was admitted to hospital on May 15, 2007, with a diagnosis of hypersensitivity vasculitis secondary to preoperative cefazolin, aggravated by postoperative cephalexin. She received a 5-day course of corticosteroids in hospital before her discharge on May 20, 2007 (Table 1). Four days after discharge, a tapering dose of prednisone was initiated for persistence of the rash (Table 1).

The patient's INR had been stable while she was taking 28 mg of warfarin per week, before initiation of the second course of prednisone therapy (Table 1). On day 6 of the second course of prednisone therapy, her INR was 2.4, but by day 13, her INR had increased to 6.1. The patient was a nonsmoker and denied use of any medications other than warfarin and prednisone, including nonprescription medications, herbal products, and supplements. Her dietary intake of vitamin K had not changed, nor had she consumed any alcohol in the previous 3 weeks. She had no symptoms of acute illness, such as diarrhea or vomiting. Her level of activity had been increasing over the previous week as she recovered after the hysterectomy and her vasculitic reaction began to subside. On day 13 of the second course of prednisone, this drug was discontinued, and the warfarin was held for 1 day. The following day, the patient's INR had increased to 7.0. Warfarin was again held for 1 day, and 1 mg of vitamin K was administered orally. The next day, the patient's INR was 1.5, and warfarin was reinitiated. At the time of writing,

*Verbal consent was obtained from the patient to publish this case.

Table 1. Timeline for Warfarin Dosing and Monitoring

Date in 2007	INR*	Weekly Warfarin Dose (mg)	Other Information
May 13	2.3	28	
May 15	ND	28	Patient admitted to hospital; prednisone started and given for 5 days
May 20	ND	28	Patient discharged from hospital
May 22	2.2	28	
May 25	2.5	28	Prednisone restarted with intended administration of the following tapering regimen: 50 mg PO for 7 days, then 40 mg PO for 3 days, then 30 mg PO for 3 days, then 20 mg PO for 3 days, then 10 mg PO for 3 days
May 30	2.4	28	Prednisone tapering schedule continued (as above)
June 6	6.1	28	Warfarin held for 2 days; prednisone tapering regimen discontinued
June 7	7.0	0	Vitamin K 1 mg PO (one dose)
June 8	1.5	20	
June 11	1.8	28	
June 27	1.9	28	
July 18	2.4	32	
August 7	1.7	32	

INR = international normalized ratio, ND = not done.

*All values determined with a CoaguChek XS point-of-care prothrombin time – INR device (Roche Diagnostics, Laval, Quebec).

in early 2008, the patient was receiving a weekly dose of 32 mg of warfarin and her condition was stable.

DISCUSSION

The interaction between warfarin and prednisone described here scored 4 on the Drug Interaction Probability Scale, which corresponds to a “possible” interaction.² This drug–drug interaction is not well recognized, possibly because reports of a potential interaction between vitamin K antagonists and oral corticosteroids have been inconsistent. The earliest reports, both published in the 1950s, suggested inhibition of dicumarol and ethyl biscoumacetate activity by prednisone and cortisone, respectively.^{3,4} The relevance of these findings is unclear, however, as vitamin K antagonists other than warfarin were used by the patients described in each report, and no studies published since then have supported a reduction in INR when steroids are added to warfarin therapy. Instead, more recent case reports support the possibility of potentiation of the effect of warfarin when corticosteroids are added to warfarin therapy.^{5,7} In addition to these case reports, a prospective trial of 10 patients receiving vitamin K antagonists documented an increase in the INR of all patients, from a mean of 2.75 (range 2.02 to 3.81) to a mean of 8.04 (range 5.32 to 20) between 29 and 156 h after receiving a 500-mg or 1-g IV infusion of

methylprednisolone.⁸ The applicability of these findings to the case described here is limited, as all of the patients received a single, large dose of methylprednisolone instead of smaller daily doses. Also, the vitamin K antagonists studied were fluindione (8 patients) and acenocumarol (2 patients), not warfarin.

The most relevant report to our own is a recent case series of 32 patients taking a stable dose of warfarin.⁹ In that study, 29 (91%) of the patients experienced an increase in INR after oral corticosteroid therapy was initiated. The average increase was 1.24 (95% confidence interval 0.86 to 1.62) occurring a mean of 6.7 days (standard deviation 3.3 days) after initiation of therapy with either prednisone (16 of the patients) or methylprednisolone (the other 16 patients). A dosage modification (dose reduced or withheld) was required for half of the patients after initiation of the corticosteroid. Five patients had INR values greater than 5 within 11 days of starting corticosteroid therapy.

The mechanism by which prednisone may interact with warfarin has not been elucidated, but it may involve inhibition of catabolism of warfarin through competition for enzymes in the CYP3A4 pathway.⁸ The metabolism of warfarin is mediated through several other cytochrome P450 pathways, including the CYP1A2, CYP2D6, and CYP2C9 pathways. Genetic deficiencies in one or more of these other pathways may result in a greater reliance



on the CYP3A4 pathway, making some individuals more susceptible to this interaction.¹⁰

Two factors about the case described here deserve emphasis from a clinical standpoint. First, the degree to which prednisone interacted with warfarin was substantial. In contrast to the largest case series describing this potential interaction,⁹ which suggested an average increase in INR of 1.24, the INR in our case increased by nearly 5. Thus, because of the potential magnitude of the interaction, it is important for clinicians to perform appropriate follow-up when warfarin and prednisone are prescribed together. Second, the patient took prednisone with warfarin over 2 separate periods, and both times there was no measured effect on the INR after 5 to 7 days. It was only after 13 days (during the second course of prednisone therapy) that prolongation of INR was detected. This apparent delay in manifestation may be another reason why this particular interaction is not well described. Prednisone is often prescribed for periods of only 5 to 7 days, which may be insufficient to cause an interaction in all patients. In any case, clinicians should be aware that a single check of the INR within 1 week after initiation of prednisone may be inadequate to detect a possible interaction.

CONCLUSIONS

Clinicians should be aware of the potential for prednisone to enhance the effect of warfarin, as indicated by the INR. The interaction may take more than a week to manifest and may be associated with a marked increase in the INR.

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