Continuation of Warfarin-Nafcillin Interaction During Dicloxacillin Therapy

A. Thomas Taylor, PharmD; Deborah C. Pritchard, RPh; Adam O. Goldstein, MD; and James L. Fletcher, Jr, MD

Athens and Augusta, Georgia; Chapel Hill, North Carolina; and Cape Girardeau, Missouri

Interactions between warfarin and penicillins have been infrequently reported. A case report of a single patient who experienced the effects of a warfarin-nafcillin interaction as well as a warfarin-dicloxacillin interaction is presented. Clinical effects of this interaction were documented primarily through changes in prothrombin time (PT) and the need for higher warfarin dosing. While the patient received nafcillin, warfarin doses were increased to as much as 4.5 times the previous amounts needed to provide adequate anticoagulation. During dicloxacillin therapy, warfarin doses were gradually decreased, but stabilized to a maintenance dose higher than the patient's pre-nafcillin dose. The dicloxacillin-warfarin interaction appears similar to that noted during nafcillin-warfarin combination.

Key words. Warfarin; nafcillin; dicloxacillin; drug interactions. (*J Fam Pract 1994; 39:182-185*)

A major concern facing physicians in achieving adequate warfarin dosing is the potential interaction of warfarin with various drugs. Mechanisms of action for these interactions include impaired absorption of warfarin, displacement of albumin-bound warfarin, and increased metabolism of warfarin. Inducement of hepatic enzymes by certain drugs causes increased metabolism of warfarin and leads to warfarin resistance.[1] Drugs that have been involved in this interaction include sedatives (eg, glutethimide, meprobamate, and ethchlorvynol), anticonvulsants (eg, barbiturates, primidone, and carbamazepine), and antimicrobials (eg, griseofulvin, rifampin, nafcillin, and dicloxacillin).[1–9] This report demonstrates the interactions of warfarin with nafcillin and warfarin with dicloxacillin in a single patient.

Submitted, revised, April 18, 1994.

From the Department of Pharmacy Practice, University of Georgia College of Pharmacy, Athens, and the Departments of Internal Medicine and Family Medicine, Medical College of Georgia, Augusta (A.T.T.); the UGA/MCG Clinical Pharmacy Program, Medical College of Georgia, Augusta (D.C.P.); the Department of Family Medicine, University of North Carolina, Chapel Hill (A.O.G.); and Cape Girardeau, Missouri (J.L.F.). At the time of this research, Drs Goldstein and Fletcher were affiliated with the Department of Family Medicine, Medical College of Georgia, Augusta. Requests for reprints should be addressed to A. Thomas Taylor, PharmD, Department of Family Medicine, FI-1081 Medical College of Georgia, Augusta, GA 30912-2390.

ISSN 0094-3509

Case Report

A 31-year-old man with a history of rheumatic fever and four aortic valve replacements was admitted to the hospital with a diagnosis of acute bacterial endocarditis. He had been in his usual state of good health before admission. Serum laboratory values obtained at admission included total protein of 8.2 g/dL (82 g/L) and albumin of 4.3 g/dL (43 g/L); both values are within normal limits. Medications at admission were triamterene 50 mg/hydrochlorothiazide 25 mg daily, atenolol 50 mg daily, dipyridamole 100 mg four times daily, and warfarin 10 mg daily. At admission, nafcillin 2 g intravenously (IV) every 6 hours and gentamicin 90 mg IV every 8 hours were begun. Two days later nafcillin was discontinued and vancomycin 1 g IV every 12 hours and oral rifampin 300 mg every 12 hours were started. Gentamicin was increased at that time to 110 mg IV every 8 hours. Three days later vancomycin and rifampin were discontinued, and nafcillin was restarted at 2 g IV every 4 hours. Nafcillin was continued at this dosage for the remainder of the patient's hospital stay. The patient's prothrombin times (PTs) gradually decreased from 21.6 seconds at admission to 13.3 seconds 9 days later. To keep the PT at a therapeutic level, the warfarin dosage was increased from 10 mg/d to an average of 30 mg/d and a maximum of 45 mg/d during nafcillin therapy (Figure).

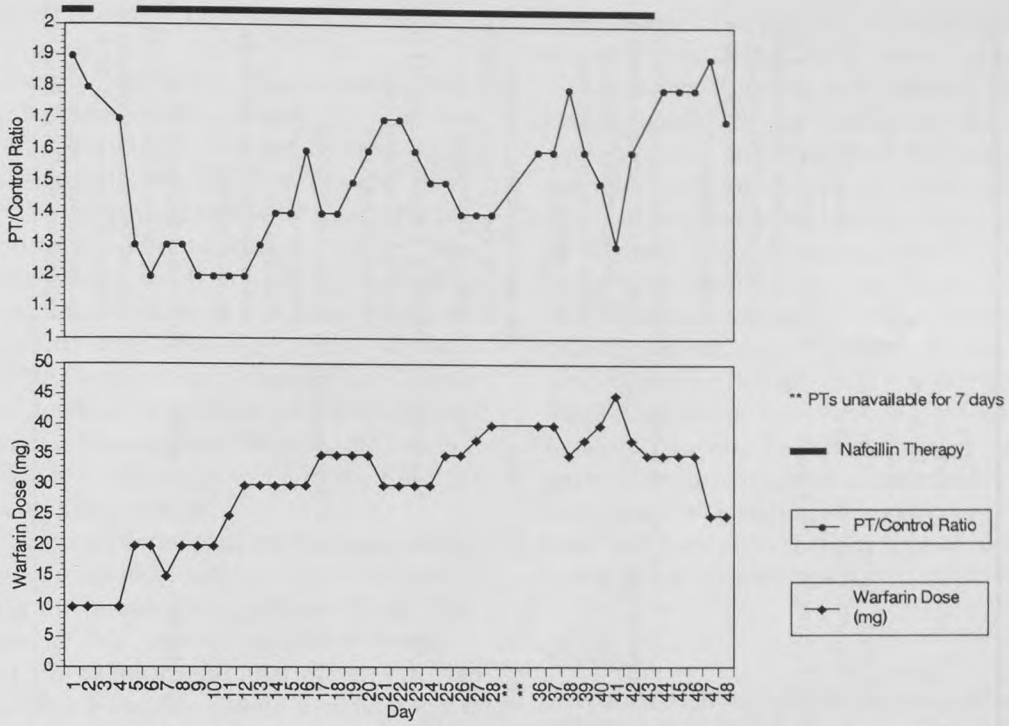

Figure. Warfarin-nafcillin interactions in a patient are documented by charts showing level of warfarin doses being increased in response to changes in prothrombin time (PT). To keep PT at therapeutic levels, warfarin was increased as much as 4.5 times the previous amounts needed to provide adequate anticoagulation. Patient was also treated with dicloxacillin and the dicloxacillin-warfarin interaction appeared similar to the nafcillin-warfarin combination.

At the time of discharge the patient was taking warfarin 35 mg/d. Other discharge medications were atenolol 50 mg/d, triamterene 50 mg/hydrochlorothiazide 25 mg daily, dipyridamole 100 mg four times daily, tocainide 600 mg three times daily, probenecid 1 g twice daily, and dicloxacillin 1 g four times daily. Four days later, the patient's warfarin dosage was decreased to 25 mg/d because of rising PTs. One week later, the warfarin dosage was changed to 20 to 25 mg/d with continued frequent PT testing. Approximately 2 months after nafcillin was discontinued, the warfarin dosage was able to be decreased to 15 mg/d.

For 4 years following discharge, the patient continued to receive dicloxacillin 4 g/d. During this period, the warfarin dosage remained at 15 mg/d, never returning to the pre-nafcillin dosage level (10 mg). This is most likely attributable to continued dicloxacillin therapy.

Discussion

A number of factors are important in the evaluation of prothrombin times, one of which is nutritional status. However, our patient's nutritional status was never in question. Since he had a normal serum albumin and total protein, the patient remained on a regular diet during his entire hospital stay.

Several case reports from the literature indicating interactions between warfarin and nafcillin are presented in the Table. In high therapeutic doses, nafcillin may cause hepatic microsomal enzyme induction.[2,5] In all cases reported to date, warfarin resistance has appeared over a period of several days of nafcillin therapy and slowly disappeared after nafcillin was discontinued. This pattern is strongly indicative of enhanced metabolism by hepatic microsomal enzyme induction.[2,5] A decrease in the elimination half-life of warfarin during nafcillin therapy also supports this theory.[5] Effects of enzyme induction are generally noted after new enzymes are synthesized, a condition dependent on the steady-state concentration of the enzyme-inducing drug.

For drugs with a short half-life, new steady-state concentrations are reached in less time than for drugs with a longer half-life. For example, the half-life of rifampin is 0.5 to 4.0 hours. With this relatively short half-life, rifampin's maximal effect on warfarin concentration occurs within 4 days after concomitant therapy is begun. However, the maximal effect on PT occurs approximately 5

Table. Case Reports from the Literature Demonstrating Varfarin-Nafcillin Interaction

Patient Age (y)/ Sex	Primary Diagnosis	Maintenance Dosage of Warfarin	PT with Maintenance Dosage	Antibiotic and Dosage	Warfarin Dosage Range During Antibiotic Therapy	Warfarin Dosage Postantibiotic	Time for Warfarin Dose to Return to Maintenance or Normal Level	Comments
29/M	Aortic valve replacement	12.5 mg/d	—	Nafcillin 2 g IV q4h	12.5–25 mg/d	10–12.5 mg/d	4 weeks	Warfarin t½ while on nafcillin was 11 h. Eight months after nafcillin was discontinued, t½ was 44 h. Nafcillin had no effect on protein binding of warfarin.*
10/F	Aortic valve replacement	Not applicable	—	Nafcillin 750 mg IV q6h	2.5–7.5 mg/d	5 mg and 2.5 mg on alternate days	~4 weeks	Warfarin concentration studies were done. The t½ increased from 5.3 hrs during nafcillin therapy to 14.5 h after the nafcillin was discontinued.†
61/M	Aortic valve replacement	5 mg/d	—	Nafcillin 2 g IV q4h	5–17.5 mg/d	5 mg/d	8 days	Average dose during antibiotic therapy was 15 mg/d. Maximum dose was 17.5 mg/d.‡
63/M	Aortic valve replacement	5 mg/d	18–21 sec	Nafcillin 1.5 g IV q4h	5–15 mg/d	5 mg/d	Not stated	Despite 2.5 mg/d increases, PT did not reach 17 sec until dose reached 15 mg/d.‡
71/M	Aortic valve replacement	2.5–5 mg/d	22–34 sec	Nafcillin 2 g IV q4h (later decreased to 2 g q6h)	5–10 mg/d	5 mg/d	See comments	6 days after nafcillin was discontinued, patient was discharged on 5 mg/d. Two weeks later the PTs were 23–26 sec on 5 mg/d.‡
41/F	Deep vein thrombosis	5 mg and 7 mg on alternate days	15–17 sec (control 12 sec)	Nafcillin 2 g IV q4h	5–15 mg/d	7.5 mg/d	~3 weeks	Patient was discharged on SQ heparin and warfarin. ~3 weeks after nafcillin was discontinued, patient's PT rose to 15.8–17.2 sec and the sole anticoagulant required was warfarin 7.5 mg/d.§

**Data from Davis et al[3]; †Shovick and Rihn[4]; ‡Fraser et al.[5]; and §Katenansky et al.[6]*
PT denotes prothrombin time; t½, half-life; SQ, subcutaneous; q4h and q6h, every 4 hours and every 6 hours, respectively.

days later, following depletion of previously formed clotting factors.[3,8]

Although the time needed to produce maximal enzyme induction with nafcillin is unknown, its half-life is 0.5 to 1.0 hours, providing a new steady-state serum concentration in approximately 2.0 to 4.0 hours. Therefore, observation of our patient's PT indicates that nafcillin's induction time is similar to that of rifampin. Nine days after nafcillin therapy was begun, the maximal effect on PT was noted. In case studies cited in the Table, the warfarin dosages that were needed to achieve adequate PTs during nafcillin therapy ranged from 1.5 to 3.5 times the maintenance dosages previously reported. During the period of concomitant therapy with nafcillin, the required dosage of warfarin for our patient was 3 to 4.5 times his pre-nafcillin maintenance dosage.

For all previously reported patients, warfarin dosages were returned to pre-nafcillin levels between 1 week and 1 month following discontinuation of the antibiotic. The warfarin dosage in our patient stabilized during a 2-month period. In addition, the final warfarin dosage was greater than his pre-nafcillin dosage. This finding was probably related to continued dicloxacillin therapy.

Dicloxacillin is also believed to be an inducer of hepatic microsomal enzymes. In a study designed to measure dicloxacillin's effect on warfarin therapy, Krstenansky and associates[6] reported that the maximal decrease in PTs occurred 6 or 7 days after dicloxacillin therapy began. This period closely resembles the time frame for maximal PT effect by nafcillin (9 days after beginning therapy). Although the average PT decrease in the dicloxacillin study was only 1.9 seconds, there was a 24.3% decrease in one patient's PT, indicating the possibility of warfarin having a suboptimal hypoprothrombinemic effect in some patients. Also, the daily dicloxacillin dosage of 2 g for 7 days was relatively low and short-term.[6] Our patient's daily dosage of 4 g for an extended period could have caused greater changes in PT values and warfarin efficacy.

Sufficient evidence now indicates that nafcillin may cause clinically relevant hepatic enzyme induction.[1-5] To date, however, only one report has addressed the potential interaction of dicloxacillin and warfarin.[6] The case reported herein further demonstrates the interaction of these orally administered agents. We therefore recommend close monitoring of any patient receiving warfarin in combination with either of these antibiotics. In hospitalized patients, daily PT should be assessed during and after antibiotic therapy until the warfarin dose is stabilized. A similar procedure should be maintained for ambulatory patients. However, because of obvious differences in the management of ambulatory patients, clinical indications of bleeding should be reviewed thoroughly with each patient so that any sign of bleeding is brought to the physician's attention.

References

1. Peterson CE, Kwaan HC. Current concepts of warfarin therapy. Arch Intern Med 1986; 146:581–4.
2. Qureshi GD, Reinders TP, Somori GJ, Evans HJ. Warfarin resistance with nafcillin therapy. Ann Intern Med 1984; 100:527–9.
3. Davis RL, Berman W Jr, Wernly JA, Kelly HW. Warfarin-nafcillin interaction. J Pediatr 1991; 118:300–3.
4. Shovick VA, Rihn TL. Decreased hypoprothrombinemic response to warfarin secondary to the warfarin-nafcillin interaction. DICP Ann Pharmacother 1991; 25:598–9.
5. Fraser GL, Miller M, Kane K. Warfarin resistance associated with nafcillin therapy. Am J Med 1989; 87:237–8.
6. Krstenansky PM, Jones WN, Garewal HS. Effect of dicloxacillin sodium on the hypoprothrombinemic response to warfarin sodium. Clin Pharm 1987; 6:804–6.
7. Romankiewicz JA, Ehrman M. Rifampin and warfarin: a drug interaction. Ann Intern Med 1975; 82:224–5.
8. O'Reilly RA. Interaction of sodium warfarin and rifampin: studies in man. Ann Intern Med 1974; 81:337–40.
9. O'Reilly RA. Interaction of chronic daily warfarin therapy and rifampin. Ann Intern Med 1975; 83:506–8.