CASE REPORT

Prolongation of Prothrombin Time with the Use of Piroxicam and Warfarin

Louise Mallet and James W. Cooper

INTRODUCTION

Piroxicam, a nonsteroidal anti-inflammatory drug is extensively prescribed for the treatment of rheumatoid arthritis and osteoarthritis in the elderly.[1,2] Reports of interactions between piroxicam and warfarin are scarce.[3] We describe the case of a probable drug interaction between piroxicam and warfarin causing a prolongation of the prothrombin time.

CASE

The patient was an 87-year-old white female living in a long term care facility. She had a history of chronic atrial fibrillation, and stroke with left hemiplegia. She had no documented allergies and was taking the following medications p.o. regularly: warfarin 5 mg daily, digoxin 0.125 mg daily, furosemide 40 mg daily, nifedipine 10 mg three times daily and triazolam 0.25 mg at bedtime when needed for sleep. To our knowledge, this patient did not have any previous history of adverse drug reactions. Prothrombin times were measured using rabbit brain thromboplastin.

From February 18 to March 24 1988, the patient's prothrombin times and prothrombin/control ratios (PT/C) were stable at 16.5 seconds (control 12 seconds, PT/C 1.4), 17.4 seconds (control 12.4 seconds, PT/C 1.4), and 18.1 seconds (control 11.2 seconds, PT/C 1.6) respectively. Laboratory values were within normal limits, with the exception of a serum albumin level which was on the lower limit of normal 38 g/L (normal: 35 to 55 g/L). Calculated creatinine clearance using the Cockcroft and Gault formula was 0,93 mL second.[4]

Piroxicam 20 mg per day was prescribed on April 10, 1988 because the patient was complaining of pain in her left arm. On April 14, the patient's prothrombin time increased to 24.9 seconds (control 10.8 seconds PT/C 2.3), without any changes in her current diet or drug therapy. No nutritional supplements were added to her diet. Seven days later, on April 21, warfarin 5 mg was held for two days and the dose of warfarin decreased to 2,5 mg alternating with warfarin 5 mg every other day. Piroxicam's therapy remained the same. Over a period of three weeks, the prothrombin times fluctuated between 22.7 seconds (control 12.3 seconds, PT/C 1.8), 24.1 seconds (control 10.7 seconds, PT/C 2.4) and 23.5 seconds (control 10.4 seconds, PT/C 2.3).

On May 19, 1988 piroxicam was discontinued and the warfarin dose was changed to 2.5 mg daily. The patient's prothrombin times fell to 13.5 seconds (control 10.9 seconds, PT/C 1.2), 14.2 seconds (control 12.2 seconds, PT/C 1.2), and 12.4 seconds (control 12.3 seconds PT/C 1.0) from May 26 through June 8, 1988. On June 17, the warfarin does was increased to 2.5 mg alternating with warfarin 5 mg every other day. Prothrombin times returned to the therapeutic range of 1.5 to 1.7 times control for the next month.

DISCUSSION

To our knowledge, only one case of piroxicam-warfarin interaction has been documented in the literature.[3] The patient, a 60-year-old man was receiving warfarin 20 mg per week, piroxicam 20 mg every day, and

Louise Mallet, Pharm.D., Assistant Professor, Campbell University School of Pharmacy, P.O. Box 1090, Buies Creek, NC 27506 and Clinical Pharmacist Methodist Retirement Home, 2616 Erwin Road, Durham, NC 27705.
James W. Cooper, Ph.D., Professor and Chairman, Department of Pharmacy Practice, College of Pharmacy, University of Georgia, Athens, GA 30602.
Address correspondence to: Louise Mallet at Campbell University School of Pharmacy above.

flurazepam 15 mg as needed for sleep. When piroxicam was discontinued, the ratio of prothrombin time to control fell to 1.3 from a range of 1.7 to 1.9 times control. Two re-challenges were done over a 10-month period which showed an increase in prothrombin time after starting piroxicam and a decrease in prothrombin time on stopping piroxicam. No severe gastrointestinal bleeding was observed in either case.

In our patient, the ratio of the prothrombin times increased to 2.3 from a range of 1.4 to 1.6 times control only four days after the introduction of piroxicam. The patient was not re-challenged with piroxicam due to the patient's age and the increased risk of bleeding.

The mechanism of this interaction is not fully understood. It has been postulated that impaired metabolism of warfarin, displacement of warfarin from plasma-protein binding sites, or both mechanisms may be responsible for this interaction.[3] Piroxicam and warfarin are greater than 97 percent bound to albumin.[2,5] A displacement of warfarin from its binding site by piroxicam may be responsible for the observed prolongation of the prothrombin time in this patient. Using an *in vitro* model, Hobbs et al reported that neither piroxicam nor dicoumarol binding was influenced by the presence of the other drug. However, this model cannot be used to explain the interaction described in our patient since warfarin was used, not dicoumarol, and these drugs have different chemical structures.[5] The displacement of warfarin from binding sites on plasma proteins by piroxicam has not been studied using the *in vitro* model used by Hobbs. It should be noted that these *in vitro* studies have some limitations; they are conducted as a nonphysiologic temperature or pH, with low protein concentrations and artificial buffer systems and with high drug concentrations. These studies are often of limited predictive value for the clinical situation.[5]

Warfarin is a racemic mixture of two enantiomers: S-warfarin and R-warfarin.[7,8] Each enantiomer in the racemic mixture of warfarin has different protein binding specificity. Certain drug interactions with racemates are stereospecific. Phenylbutazone increases the anticoagulant effect of warfarin by inhibiting the metabolism of the more potent S-enantiomer while having little effect on the metabolism of the R-form.[9] The effect of piroxicam on the enantiomers of warfarin has not yet been studied and may play an important role in this interaction. The interaction between dicoumarol and piroxicam cannot be extrapolated to warfarin because of the different activity of the enantiomers.

CONCLUSION

Piroxicam should be used with extreme caution in patients receiving warfarin. The intensity of anticoagulation should be monitored very closely when piroxicam is added to warfarin therapy; the dose of warfarin may need to be adjusted accordingly. Further studies are needed to document and explain the mechanisms of the interaction between piroxicam and warfarin.

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