Interaction of Rifampin and Warfarin*

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A 72-year-old man who had been taking rifampin daily for several months was concurrently administered warfarin daily for ten weeks. During this period, the prothrombin time (PT) rose remarkably little as the dosage of warfarin was increased. With difficulty, satisfactory anticoagulation was achieved by giving warfarin 20 mg daily. On discontinuation of rifampin therapy, the PT increased significantly, and subsequent stabilization of the PT within therapeutic range required treatment with warfarin 7.5 mg daily.

Rifampin has been reported to decrease the response to orally administered anticoagulants.1,2 This effect, to the best of our knowledge, has not been well documented clinically with the use of warfarin. Described in this report is a patient who responded minimally to increasing dosage of warfarin while concurrently receiving rifampin. When rifampin therapy was discontinued, the prothrombin time (PT) increased dramatically after one week.

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Case Report

The patient, a 72-year-old man, was admitted to the West Tennessee Chest Hospital on April 14, 1974 with symptoms of congestive heart failure. In August, 1973 the patient was told he had pulmonary tuberculosis and was hospitalized for four months. His only medication since December, 1973 was rifampin 600 mg daily and ethambutol 1,000 mg daily. Prior chest x-ray films had shown borderline cardiomegaly, and he had labile hypertension during the earlier hospitalization. Examination showed blood pressure 110/60 mm Hg, pulse rate 116 per min, respiration rate 36 per min, and weight 52.4 kg. He was in mild respiratory distress and slightly confused. Other findings were a hepatomegaly, dullness and râles in the right lower portion of the chest, pulsus alternans, and an S3 gallop. The liver was enlarged; chest x-ray films confirmed cardiomegaly and right pleural effusion. Mild pre-thalamic edema was present; distal and radial pulses were absent. Electrocardiogram revealed sinus tachycardia and abnormal ST-T changes. Laboratory data included the following: hematocrit, 39 percent; white blood cell count, 6,400/cu mm; serum sodium, 134 mEq/liter; potassium, 4.3 mEq/liter; chlorides, 106 mEq/liter; and bicarbonate, 14 mEq/L; blood urea nitrogen, 76 mg percent; creatinine, 3.6 mg percent; calcium, 3.0 mEq/liter; phosphorus, 3.4 mEq/liter; total protein, 7.4 gm percent; albumin, 3.0 gm percent; and serum thyroxine, 4.7 percent.

The patient was initially treated for congestive heart failure with digitalis and diuretics and with heparin as an anticoagulant for suspected pulmonary emboli. There was difficulty in controlling the congestive heart failure shortly after admission to the hospital. His condition was worse on April 26 and pulmonary edema developed on May 2. Serum calcium levels were repeatedly 1.8-2.4 mEq/liter, and he was given vitamin D 50,000 units daily, after which the calcium levels increased to 4.4 mEq/liter. Since May 22 his cardiac classification has been class 3C, and the serum creatinine value decreased to 1.6 mg percent. Therapy with rifampin 600 mg daily and ethambutol 1,000 mg daily was continued.

![Graph: Interaction of Rifampin and Warfarin](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20964/ on 06/26/2017)

**Figure 1.** Response to treatment with warfarin while concurrently receiving rifampin 600 mg daily and after rifampin therapy was discontinued.
from the first day of hospitalization.

After initial anticoagulant treatment with heparin, the therapy was converted to warfarin. The patient’s response to administration of warfarin is depicted in Figure 1. In general, repeated increases in warfarin dosage resulted in only small increases in the PT as long as rifampin was being administered. Only May 3, a PT of 30.8 seconds (patient)/12.8 seconds (control) was reported. This response came 72 hours after a 35-mg dose of warfarin. The PT on May 13 was 26.9/13.4 (an increase of 10.1 seconds from the previous day); no obvious explanation for this increase could be determined. Beginning May 22, the dosage of warfarin was gradually increased, but the PT rose remarkably little until June 13 when it increased to 22.4/11.4. This relatively sudden rise was most probably due to the oral administration of quinidine 1 gm on June 10. Quinidine has been reported to enhance the action of warfarin.3,4 By June 19 the PT had decreased to 16.9/11.4, and by July 1, although the patient was receiving 20 mg warfarin daily, the PT was 23.9/12.1.

Administration of rifampin 600 mg daily was discontinued after the 8 AM dose on June 30, and isoniazid 300 mg daily was initiated; therapy with warfarin 20 mg daily and ethambutol 1,000 mg daily was continued. By July 5 the PT had risen only to 23.8/11.5, so on July 8 the PT was 37.5/11.6. Phytonadione 15 mg was given orally on July 8 and by the next day the PT had dropped to 18.1/11.9. Warfarin treatment 15 mg daily was started on July 8, and in five days the PT was 36.9/12.9. Warfarin was not administered July 15 and 16. On July 16 a PT of 41.6/11.6 was reported, and by the following day the PT was 23.4/11.4. Liver function was checked and found to be within normal limits. Warfarin therapy 7.5 mg daily was begun on July 17 and was maintained because it provided adequate anticoagulation.

**DISCUSSION**

Michot et al describe the inhibition of the activity of acenocumarol, a coumarin anticoagulant, by rifampin. This study is possibly the primary basis for the statements regarding the interaction potential of rifampin and orally administered anticoagulants made by Vall-Spinosa and Lester and by the pharmaceutical manufacturers of rifampin. Nitti et al suggest that rifampin may have an enzyme-inducing effect. The possibility that rifampin may increase the metabolic rate of orally administered anticoagulants is appealing as a possible mechanism for this interaction because the PT was not significantly increased for eight days after discontinuation of rifampin. O’Reilly states that treatment with rifampin may enhance the excretion of warfarin. However, the mechanism for this interaction remains to be clearly defined.

While our patient was receiving rifampin, the PT rose little with increasing dosage of warfarin. However, after discontinuation of rifampin therapy, a significant increase in warfarin activity was seen. When the patient was not receiving rifampin, satisfactory anticoagulation was achieved with administration of warfarin 7.5 mg daily.

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**REFERENCES**


**Hypertrophic Subaortic Stenosis Complicated by High Degree Heart Block: Successful Treatment with an Atrial Synchronous Ventricular Pacemaker**

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The development of high degree atrioventricular block in a patient with hypertrophic subaortic stenosis underscores the importance of a properly timed atrial contraction in this disorder. Atrial synchronous ventricular pacing therapy, by providing reliably timed atrial systole and increased left ventricular end-diastolic volume, has an important role in this patient and in similar cases.

Variations in the functional subvalvular gradient seen in hypertrophic subaortic stenosis have been the subject of a number of fascinating and important studies which have provided both an understanding of the pathophysiology of the outflow obstruction and the rationale for therapy and management of this disorder.1-7 Specifically, left ventricular outflow obstruction, related to systolic apposition of the anterior mitral leaflet and the interventricular septum, is augmented by increasing the inotropic state, decreasing left ventricular volume, or decreasing aortic pressure. In addition to the abnormal pathophysiology present during systole, the importance of abnormal diastolic compliance in hypertrophic subaortic stenosis has been emphasized.4 Thus, the apparent increase in muscle “stiffness” and associated resistance to passive diastolic filling of the left

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