Case Report

To achieve target international normalized ratio with concurrent warfarin and rifampicin therapy is a challenge: a case report and review of literature

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ABSTRACT

A 60-year-old man with a history of deep vein thrombosis put on anticoagulation therapy with warfarin 2 mg daily. Achieving a therapeutic level of anticoagulation was difficult despite escalating doses of warfarin, because of the interaction with rifampicin. A 5 to 6 fold increase in warfarin dose was prescribed to reach therapeutic international normalized ratios (INRs), but even these increases were insufficient to maintain his INR in the therapeutic range. After rifampicin was discontinued, warfarin doses were gradually reduced over the next 2 months. When concurrent warfarin-rifampicin therapy is necessary, vigilant monitoring of INR is imperative and rifampicin should be stopped. Warfarin is an oral anticoagulant used to get target INR to prevent thrombosis in various cardiovascular diseases. Its metabolism is affected by dugs, diet and individual characteristics. It is metabolized in liver by microsomal cytochrome P450 enzyme. Rifampicin is an essential component of first line antitubercular regimen. It induces enzyme P450, responsible for metabolism of warfarin. So to get target INR 2.5 to 3.5 is very difficult even with maximum possible dose of warfarin when patient taking simultaneously both drugs. In this case, rifampicin was stopped to achieve target INR. Tuberculosis patient on warfarin should not take rifampicin as component of first line antitubercular regimen.

Keywords: Warfarin, Rifampicin, Deep vein thrombosis, Drug interaction

INTRODUCTION

Warfarin is used in the prevention of thrombosis and thromboembolism. It is the most widely prescribed oral anticoagulant worldwide. Despite its effectiveness, treatment with warfarin has many challenges. Many commonly used drugs interact with warfarin, as do some common foods containing vitamin K1.[1] So its activity has to be closely monitored by the international normalized ratio (INR) to ensure target value. Proper and safe dose of warfarin is essentially needed. A high INR predisposes patients to an increased risk of bleeding, while an INR below the therapeutic target indicates insufficient dose

for prevention of thromboembolism.[2] Warfarin decreases blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K1 to reduced form produced during carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Thus warfarin inhibits the vitamin K-dependent synthesis of biologically active forms of the clotting factors II, VII, IX and X, as well as the regulatory factors protein C and protein S.[3] Despite being labeled a vitamin K antagonist, warfarin does not antagonize the action of vitamin K1, but rather antagonizes vitamin K1 recycling, depleting active vitamin K1.[4,5] Thus, the pharmacologic action may always be reversed by fresh vitamin K1. When

administered, onset of their effect requires about two to three days before remaining active clotting factors have had time to naturally disappear in metabolism, and the vitamin K.

K1 requires a similar period of time.[6] Warfarin is best suited for anticoagulation in areas of slowly running blood. Drugs or food interactions may enhance or reduce warfarin's anticoagulation effect. To optimize the therapeutic effect without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required by plasma INR. During the initial stage of treatment, INR is checked daily; intervals between tests can be lengthened if the patient manages stable therapeutic INR levels on an unchanged warfarin dose. The target INR level varies from case to case depending on the clinical indicators, but tends to be 2–3 in most conditions.[7,8] In addition, for the first three days of "warfarinization", the levels of protein C and protein S decrease faster than procoagulation proteins such as factor II, VII, IX, and X. Warfarin is a coumarin derivative. Racemic warfarin accumulates in the liver, in which both the R and the S enantiomers are metabolized by different pathways. The S enantiomer is approximately 90% oxidatively metabolized, primarily by the CYP2C9 isoenzyme of the CYP system and, to a lesser extent, by CYP3A4. The less potent R enantiomer is approximately 60% oxidatively metabolized, primarily by the two CYP isoenzymes CYP1A2 and CYP3A4 and, to a lesser extent, by CYP2C19.[10-12]

Rifampicin is one of the first-line drugs used to treat tuberculosis (TB). It is also a potent inducer of the hepatic cytochrome P-450 (CYP) oxidative isoenzymes system and the P-glycoprotein transport system.[13] The acceleration of drug metabolism due to CYP induction by rifampicin may compromise the therapeutic efficacy of several drugs. There are several well-documented examples of clinically significant drug-drug interactions during rifampicin therapy, including clinically significant interactions between warfarin and rifampicin.[13,14]

Rifampicin is known to reduce the effect of warfarin on prothrombin activity. This drug-drug interaction has been described in individual case reports and pharmacokinetic studies.[15] The effect of the rifampicin-warfarin interaction on the anticoagulant response can be tested using INR, which is the current standard for monitoring warfarin responses. Patients with sub- and supratherapeutic INR values are at a higher risk of clinical complications respectively thrombosis and bleeding.

I report a case of deep vein thrombosis with co-administration of rifampicin and warfarin and detail the challenges related to international normalized ratio (INR) monitoring and target value achievement.

CASE REPORT

A 60 years old patient presented with erythematous patch over right leg and moderate grade fever and difficulty in breathing. He had also mild pain in right leg. His routine investigations were within normal limits except highly raised ESR (120 mm/hr) and strongly positive Mantoux test (30x40mm). He had also digital chest x-ray and CT chest; both did not favor consolidation or any lung mass. However due to persistent long standing fever with highly praised ESR and strongly positive Mantoux test, probable diagnosis of tuberculosis was made in Indian context and patient was put on antituberculosis treatment (ATT) first line regimen containing drugs rifampicin, isoniazid, ethambutol and pyrazinamide. During treatment with ATT, he had no improvement and his leg pain worsened and also developed large erythematous lesion at the site of pain. Then he consulted cardiologist and he had Doppler study of the right lower extremity and revealed venous blockage at multiple levels.

Patient was put on warfarin 2mg/day and every day PT and INR were done. When target value of INR 2- 3 was not achieved after five days ,then every day 2mg increment of dose was done but when target value did not achieved after dose of 10 mg and at the same time patient clinical condition was continuously deteriorating , he consulted clinical hematologist . The hematologist advised to stop rifampicin and he achieved the target value with dose of 4 mg only in 5 days.

DISCUSSION

Rifampicin is known to lower plasma warfarin concentrations by increasing the rate of warfarin clearance.[7] After cessation of rifampicin, prothrombin time was maintained within the same range by a 50% reduction of warfarin dose.[8] This rise in warfarin concentrations can be explained by the known mechanism by which rifampin increases warfarin clearance.[9]

The proposed mechanism for the rifampicin-warfarin interaction involves the induction of the isoenzymes CYP2C9, CYP3A4, CYP1A2 and CYP2C19, accelerating the clearance of both the R and the S enantiomers of warfarin.[12] Enzyme induction typically exhibits a slow onset and long-term recovery time. In particular, CYP induction depends on the synthesis of new drug-metabolizing enzymes, with the initial effects detectable within the first two days of concurrent therapy. However, it generally takes at least one week to observe the effects of maximal induction. The onset of CYP stimulation is also dependent on the half-life of the inducer. As rifampicin exhibits a relatively short half-life, steady-state serum concentrations are obtained faster when rifampicin is compared with other inducing drugs with longer half-lives.[13] The cessation of CYP induction after the discontinuation of rifampicin occurs gradually, depending on the drug´s elimination and the gradual

decay of the enhanced enzymatic activity in the liver. The concurrent use of isoniazid may cause an opposite effect on the liver by inhibiting CYP3A4, leading to the accumulation of the less potent R enantiomer. However this antagonizing effect is not enough to neutralize the induction effect of rifampin. As an additional mechanism, an acquired inhibition of fibrin stabilization has been associated with isoniazid therapy. In the present case, the stimulatory effect of rifampicin on the liver seemed to be clinically predominant over the effect of the concomitant use of isoniazid on the coagulation state, which is consistent with previous findings.[14,15] The prediction of a patient's response to warfarin and of the precise magnitude of the dosage adjustments required when rifampicin is initiated or discontinued is challenging.

Extensive changes in warfarin dosage are required to attain and maintain a therapeutic INR during the initiation, maintenance, and discontinuation of rifampin.

CONCLUSION

This case demonstrated the influence of rifampicin therapy on warfarin dose requirements and the increased risk of bleeding. The INR should be monitored weekly until a new stable dose is achieved after rifampicin discontinuation to prevent clinical complications related to unstable INR values. In particular, patients with cardiovascular diseases and active TB represent a group with a substantial risk of drug-drug interactions. Learning how to predict and monitor drug-drug interactions may help reduce the incidence of clinically significant adverse drug events. Patients on concurrent therapy should be rigorously monitored with regular INR checks and warfarin dosage adjustments.

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