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Challenge of deep vein thrombolysis in a patient on rifampicin for pulmonary tuberculosis

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ABSTRACT

Administration of rifampin concomitantly with drugs that undergo biotransformation through cytochrome P-450 pathway can accelerate elimination of coadministered drugs. This short case report provides an evidence of rifampicin-warfarin interaction, both of which are metabolized through cytochrome P-450 enzymes in the liver. This finding is significant to emphasize upon the need for vigilant monitoring to achieve the desired anticoagulation effect of warfarin in a patient already on long-term rifampicin, and the dose of warfarin may have to be greatly increased to achieve the desired therapeutic effect.

INTRODUCTION

The antitubercular drug Rifampin is known to induce certain cytochrome P-450 enzymes in the liver. Administration of rifampin concomitantly with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping rifampin. Treatment for deep vein thrombosis in a patient already on anitubercular regimen may prove to be extremely perplexing and difficult as presented in the following case report.

CASE REPORT

A 50 years old baker suffered 50% burn injuries and was admitted to the critical care unit. He had earlier been diagnosed to be suffering from pulmonary tuberculosis and was on a combination of isoniazid, ethambutol, rifampicin and pyrazinamide for 3 months. He recovered from his burn injuries but developed deep vein thrombosis involving the proximal vessels of right leg following prolonged immobilization in bed. There was clinical suspicion driven by increased local temperature and swelling of the leg. Venous doppler studies showed evidence of deep vein thrombosis involving right external iliac, common iliac veins, superficial femoral vein, popliteal vein and the anterio and posterio tibial veins further distally.

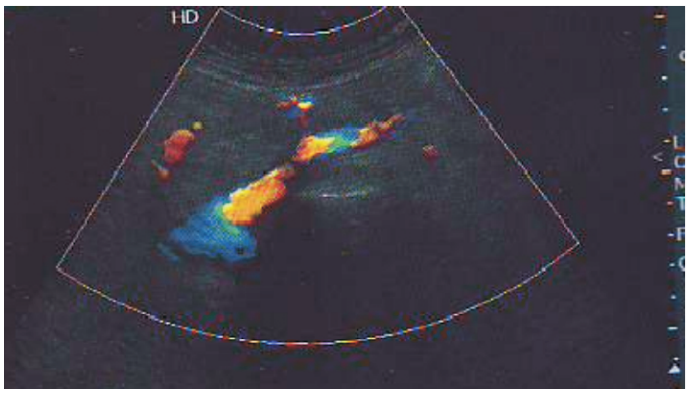

Fig 1: Venous Doppler image showing extensive deep vein thrombosis

He was started on standard anticoagulation regimen with an intravenous bolus of 5000 IU of heparin injection. Tablet acitron 2mg once daily was added to this. APTT monitoring was started and the target APTT was set at 60-80sec. Satisfactory APTT level could not be achieved after initial 96 hours of treatment onset. Venous Doppler screening showed the extent of sub-acute thrombus persisting without any sign of resolution. Dose of oral warfarin was increased to 4 mg per day. No significant improvement in the values of APTT or INR was observed. Dose of warfarin was increased to 6mg once daily. Next doppler screening study showed slight flow induced on augmentation in the right common iliac and popliteal vein. Target values of APTT

and INR were not achieved yet. Acitron dose was next titrated to 8mg/day. Simultaneous heparin infusion was continued, the dose of which was adjusted with regular APTT monitoring. 2500 IU of heparin was administered 8 hourly. Resolution of the thrombus was documented after 11 days of initiation of anticoagulation treatment. Common femoral, superficial femoral, deep femoral veins showed normal flow on venous doppler study. Inferior venacava showed normal flow and phasicity. Heparin injections were stopped after 11 days. The patient was continued on tablet warfarin 6mg once daily and LMWH 60 mg twice daily. INR was measured every alternate day. Target values for INR were never achieved at all as shown in Fig 3. However clinical improvement was documented over serial venous doppler images. The girth of the thigh reduced, pain and signs of local inflammation of the limb also disappeared and the patient became ambulatory and fit for discharge.

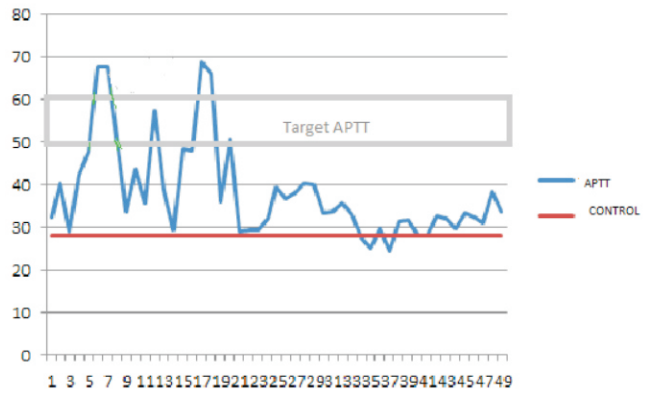

Fig 2: Variations in the APTT values measured at 2 hourly interval to titrate the dose of anticoagulation therapy.

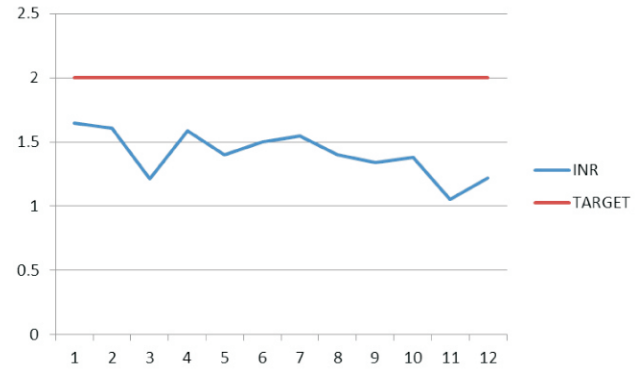

Fig 3: Variations in the INR values measured at hourly interval to monitor level of anticoagulation achieved. Inspite of clinical improvement , the target INR was never achieved.

DISCUSSION

Rifampicin is a potent inducer of drug metabolism by increasing proliferation of smooth endoplasmic reticulum and level of enzyme cytochrome P_{450} content in liver. There is selectivity in the enzyme induction effect of rifampicin for anticoagulants like warfarin leading to hypoprothrombinemic effect of the drug that can be expected from usual recommended doses. It has been reported that the requirement of anticoagulants may increase in case of concomitant use with rifampicin [1]. On the other hand, over-coagulation may develop when rifampicin is withdrawn in a patient who is maintained on warfarin [2]. Therefore it has to be noted in critical care practice that extensive modifications in warfarin dosage are required to attain and maintain desired prothrombinemic effect when used in conjunction with or during the withdrawal of rifampin.

In order to regulate and achieve required anticoagulation effect in patients receiving anticoagulants and rifampin, prothrombin time is considered to be the safe marker. The prothrombin time should be measured daily or as frequently as may be necessary to establish and maintain the desired anticoagulant effect. In case of Deep Vein Thrombosis and Pulmonary Embolism management the target value of INR has been fixed at 2.0-3.0. When the INR falls below 2.0 there is increased risk of further thrombosis while serious bleeding risk increases when the INR rises above 4.0.

Challenging clinical conditions where thrombolytic management of DVT in patients already on rifampicin has been reported earlier in literature. One study by reports a 233% increase in warfarin dosage over a period of 4 months to attain a therapeutic INR for a patient on long-term rifampin therapy, while 70% reduction in warfarin dosage over 45 weeks was also necessary to maintain a therapeutic INR after rifampin discontinuation. A 5- to 6-fold increase in warfarin dose was not sufficient to maintain therapeutic international normalized ratios (INRs) in an elderly man with DVT and PE, who was also on rifampicin has been also reported [3,4,5].

CYP2C9 has been identified as the rate-limiting enzyme in the metabolic clearance of clinically used drugs such as the tolbutamide and glipizide, phenytoin, anticoagulant warfarin, and numerous nonsteroidal anti-inflammatory drugs such as flurbiprofen, diclofenac, torsemide, and ibuprofen. Rifampicin can induce CYP2C9 mRNA, protein, and catalytic activity to enhance metabolic breakdown and clearance of warfarin from the system when both drugs are co administered.

In this short case report we have tried to provide another evidence of rifampicin-warfarin interaction with the help of graphical illustrations. Vigilant monitoring is necessary to achieve desired anticoagulation effect of warfarin in a patient already on long-term rifampicin, and the dose of warfarin may have to be greatly increased to achieve the desired therapeutic effect.

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