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Case report

[Translated article] Pharmacological interaction between rifamycins and anticoagulants: Case report

Interacción farmacológica entre rifamicinas y anticoagulantes: Caso clínico

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Introduction

Mycobacterium avium complex (MAC) microorganisms are the most common cause of non-tuberculous mycobacterial (NTM) pulmonary infection in patients with predisposing disease including asthma, emphysema, chronic obstructive pulmonary disease (COPD), and bronchiectasis.[1] Treatment of pulmonary MAC infection should be based on a combination of rifamycin, macrolide, and ethambutol.[2] Rifampicin is the most widely used rifamycin due to its extensive history of use. However, due to its potent CYP450-inducing effect, this drug is responsible for a high number of interactions, sometimes necessitating its replacement with an alternative.

We describe the case of a recipient of a mechanical heart prosthesis who was being treated with acenocoumarin and developed recurrent MAC infections. This case illustrates the challenge of combining rifamycins with anticoagulants.

Case description

A 67-year-old female patient was diagnosed with bronchiectasis in 2010 and followed up in the pulmonology unit. Since then, the patient has had recurrent infections, with the most commonly isolated microorganisms being *Escherichia coli*, methicillin-sensitive *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and MAC. Regarding MAC infections, the first isolation was obtained in a bronchoaspiration performed in 2019, prompting the decision to start treatment with rifampicin, clarithromycin, and ethambutol over 12 months. However, in early 2022, the microorganism was isolated again in the sputum sample, and the case was classified as an eradication failure. The patient was referred to the Infectious Diseases Unit for follow-up. In late 2022, MAC was again isolated in sputum, and treatment was started with rifampicin 300 mg tablets twice daily, azithromycin 500 mg daily, and ethambutol 400 mg capsules 3 times daily over 12 months.

However, in 2008, the patient had been diagnosed with atrial fibrillation, and had been treated with anticoagulants ever since. In 2011, she was diagnosed with rheumatic mitral valve disease with severe stenosis, and was being monitored by the cardiology unit. Due to progression of heart failure to New York Heart Association functional class III, she was assessed for surgery, and underwent mitral valve replacement surgery with a mechanical heart valve in 2014. Acenocoumarol was recommended as the anticoagulant drug, with doses adjusted to according to haematological controls.

A case review identified a risk of a serious interaction between rifampicin and acenocoumarol when used together (Table 1). Both drugs were administered concomitantly for 2 months without analytical monitoring, but there were no clinical manifestations. Finally, after obtaining the patient's consent and assessing the risk–benefit of the therapeutic options, the following anti-infective treatment was started: rifabutin 150 mg tablets twice daily; azithromycin 500 mg, 1 tablet with breakfast; ethambutol 400 mg, 3 tablets with lunch; and clofazimine 100 mg with breakfast. The anticoagulant treatment used belonged to the novel oral anticoagulant (NOAC) group.

Discussion

According to the guidelines of the Infectious Diseases Society of America,[2] the recommended treatment regimen for nodular-bronchiectatic infections caused by MAC is a 3-drug combination: rifampicin, azithromycin, and ethambutol administered 3 times per week (Table 2). As second-line drugs, clarithromycin has been proposed, as well as rifabutin, which is a rifamycin drug with a risk of severe interaction with coumarins and low-to-moderate interaction with NOACs (Table 1). For patients who are intolerant to the above-mentioned drugs or whose strain is resistant to them, alternative drugs are clofazimine, moxifloxacin, and linezolid. It is recommended that patients with macrolide-sensitive MAC and pulmonary disease should be treated for at least 12 months after cultures become negative.

Rifampicin is a potent enzyme inducer and inducer of drug transporters, mainly cytochrome CYP450 and P-glycoprotein (P-gp). For this reason, rifampicin can cause serious drug interactions when

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Table 1
Interactions between rifampicin and rifabutin and anticoagulants.

	Rifampicin (P-glycoprotein inducer and potent CYP3A4 inducer)	Rifabutin (moderate CYP3A4 inducer)
Apixaban	Severe[3,4] Avoid concomitant use Decreased apixaban serum concentration and increased risk of thromboembolic events Monitoring of apixaban serum concentration recommended	Less[3,4] Decreased apixaban serum concentration Overall, no action recommended
Rivaroxaban	Severe[3,4] Avoid concomitant use Decreased serum rivaroxaban concentration	Less[3,4] Decreased serum rivaroxaban concentration Overall, no action recommended
Edoxaban	Severe[3] Avoid concomitant use Decreased serum edoxaban concentration Moderate[4] Avoid concomitant use Decreased serum edoxaban concentration	No interaction
Dabigatran	Severe[3,4] Avoid concomitant use Decreased dabigatran serum concentration and increased risk of thrombosis Monitoring of dabigatran serum concentration recommended	No interaction
Warfarin	Moderate[3] Decreased anticoagulant efficacy Prothrombin time and INR monitoring recommended Dose adjustments may often be necessary Severe[4] Decreased serum concentration of vitamin K antagonists Consider alternatives to this combination when possible	Moderate[3] Decreased anticoagulant efficacy Prothrombin time monitoring recommended Dose adjustments may often be necessary Severe[4] Decreased serum concentration of vitamin K antagonists Consider alternatives to this combination when possible
Acenocoumarol	Severe[3,4] Decreased serum concentrations of vitamin K antagonists Consider alternatives to this combination when possible	Severe[3,4] Consider alternatives to this combination when possible
LMWH (Enoxaparin)	No interaction	No interaction

Abbreviations: INR, international normalised ratio; LMWH, low molecular weight heparin.

administered with CYP450 and P-gp substrates. Rifabutin is considered an alternative to rifampicin because it is a less potent inducer and has fewer drug–drug interactions.[5] Table 1 shows the documented interactions of rifampicin and rifabutin with the main anticoagulants.[3,4]

A review of the published literature revealed several clinical case reports[6,7] in which concomitant rifampicin-warfarin was maintained with close monitoring of the international normalised ratio (INR) for warfarin dose adjustment. In contrast, a patient with pulmonary thromboembolism and cerebral thrombosis on concomitant rifampicin–warfarin failed to achieve therapeutic levels of warfarin, which was replaced with edoxaban.[8]

Based on treatment recommendations for MAC, considerations of drug interactions, and evidence from published clinical cases, we propose 3 alternative treatment options:

a) First option: Combine rifabutin, azithromycin, ethambutol, and/or clofazimine together with a NOAC. However, dabigatran should not be used as it is contraindicated in patients with prosthetic heart valves, according to an information note from the Spanish Agency for Medicines and Health Products[9] and the results of the Re-ALGIN trial,[10] which concluded that dabigatran increases the risk of ischaemic stroke and thrombosis in patients with prosthetic heart valves. Low molecular weight heparins could be an option to avoid drug–drug interactions, but this was rejected in the present case as the patient objected to daily subcutaneous administration. Furthermore, with this option, the risk of QT interval prolongation associated with the co-administration of clofazimine and azithromycin must be taken into account.[3,4]
b) Second option: If the preference is to continue with a coumarin anticoagulant, the alternative would be to use a rifamycin-free regimen, such as oxifloxacin–azithromycin–ethambutol, which is less effective but also less toxic.
c) Third option: It could be assumed that the decrease in AUC (50%) of coumarins resulting from the interaction with rifampicin is offset by the increase in AUC (54%) resulting from the interaction with macrolides. Therefore, the regimen would be maintained:

Table 2
Dosage guideline for drugs used in the management of non-tuberculous mycobacterial pulmonary disease.

Drug	Daily dosage	Dosage 3 times per week	Adjustment for hepatic impairment	Adjustment for renal impairment
Rifampicin	10 mg/kg (450 mg or 600 mg)	600 mg daily	Caution	N/A
Rifabutin	150–300 mg per day (150 mg per day with clarithromycin)	300 mg per day	Caution	Reduce dose by 50% if CrCl <30 mL/min
Azithromycin	250–500 mg daily	500 mg daily	N/A	N/A
Clarithromycin	500 mg twice a day	500 mg twice a day	N/A	Reduce dose by 50% if CrCl <30 mL/min
Ethambutol	15 mg/kg per day	25 mg/kg per day	N/A	Increase dosing interval (e.g., 15–25 mg/kg, 3 times per week)
Clofazimine	100–200 mg per day	N/A	Caution in severe hepatic impairment	N/A

Abbreviations: N/A, not applicable; CrCl, creatinine clearance.

rifampicin, azithromycin, ethambutol, and acenocoumarol.[3,4] However, due to significant individual variability, very close monitoring of the INR would be necessary.

In conclusion, further studies are needed to define the optimal anticoagulation strategy for patients requiring rifamycin therapy.

Ethical responsibilities

This case report met the criteria of the International Committee of Medical Journal Editors (ICMJE).

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Author contributions

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Declaration of competing interest

None declared.

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