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CASE REPORT

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Rifampicin-Amlodipine Interaction: A Case Report of Hypertension Exacerbation

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ABSTRACT

Introduction: Rifampicin, a first-line anti-tubercular therapy drug, is a strong inducer of hepatic cytochrome P450 (CYP). Amlodipine and metoprolol, two anti-hypertensives that are CYP substrates, have the potential to interact pharmacologically with rifampicin. Therefore, individuals with hypertension receiving rifampicin-based anti-tubercular therapy are at risk for worsening hypertension.

Case Details: We report a case of a 63-year-old female patient, who developed accelerated hypertension after initiating rifampicin. Later, up to four antihypertensive drugs were administered as part of a gradual increase in dosage but did not successfully lower blood pressure to a desirable level. After clinical pharmacist intervention, Tab. Amlodipine+Metoprolol 5 mg+50 mg was discontinued and the blood pressure measurements gradually improved.

Conclusion: We postulate that rifampicin diminished the therapeutic effect of amlodipine and metoprolol and hence recommend that prudent monitoring for worsening hypertension should be carried out in hypertensive patients with chronic kidney disease receiving anti-tubercular therapy.

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Introduction

Patients with Chronic Kidney Disease (CKD) experience immunosuppression, and hence they are more vulnerable to infections (Duggal *et al.*, 2019; Syed-Ahmed *et al.*, 2019). According to the reports, people with CKD on maintenance hemodialysis have a higher incidence of tuberculosis than those with CKD at any stage (Alemu *et al.*, 2022). The majority of CKD patients have hypertension, hence concomitant treatment with anti-tubercular and antihypertensive medications is required to reduce morbidity and death (Agrawal *et al.*, 2016). According to the established protocol, patients are started on rifampicin in addition to other medications once the diagnosis of tuberculosis is confirmed (Duggal *et al.*, 2019).In the majority of CKD patients, blood pressure control is challenging, and three or more anti-hypertensives at their highest recommended doses are needed to attain tolerable blood pressure values (Duggal *et al.*, 2019). We present a case of accelerated hypertension during anti-tubercular treatment that developed in a previously well-treated hypertensive patient with CKD receiving maintenance hemodialysis.

Case presentation

A 63-year-old female presented with complaints of breathlessness that started a day ago, which was insidious in onset, gradually progressive, graded 3 on the modified Medical Research Council (mMRC) dyspnoea scale, aggravated on lying down, and relieved by standing or sitting. The patient was on maintenance hemodialysis for CKD and was a known case of hypertension and Type II diabetes mellitus. She was receiving consistent treatment with the following medications. Tab. Amlodipine + Metoprolol 5 mg + 50 mg 1-0-1, Tab. Prazosin Hydrochloride 2.5 mg 0-0-1, Inj. Insulin Aspart 7-5-0, Inj. Insulin Glargine 0-0-12, Tab. Torsemide 10 mg 1-½-0 and Tab. Sodium Bicarbonate 500 mg ½-0-½. The patient's blood pressure was 150/90 mmHg at the time of

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evaluation, and other vital signs were in the normal range. Additionally, high levels of urea and creatinine in the patient indicated diminished renal function. Bronchoscopy and Computed Tomography (CT) thorax showed focal dense consolidations and mild pleural effusion supporting the diagnosis of tuberculosis. The diagnosis of pulmonary tuberculosis was further confirmed by additional evidence from Cartridge-Based Nucleic Acid Amplification Test positive status. Following dose modification following nephrology advice, anti-tubercular treatment was initiated by Revised National Tuberculosis Control Programme recommendations along with anti-hypertensives, anti-diabetics, bicarbonates, and diuretics. Blood pressure increased one week after beginning the anti-tubercular medication. Up to four antihypertensive drugs were administered as part of a gradual increase in dosage, starting with Inj. Labetolol 10 mg slow IVSTAT, Tab. Amlodipine + Metoprolol 5 mg + 50 mg BD, Tab. Prazosin Hydrochloride 2.5 mg BD, Tab. Clonidine 0.1 mg OD. Antihypertensive therapy did not, however, successfully lower blood pressure to a desirable level. After clinical pharmacist intervention, it was evident that rifampicin decreases the effectiveness of amlodipine and metoprolol via inducing cytochrome P450 (CYP) mediated metabolism of the drugs. The causality assessment of this interaction between the drugs was determined to be "Probable". Anephrologist's opinion was sought and Tab. Dihydralazine 25 mg ½-½-½ was added after stopping Tab. Amlodipine + Metoprolol 5 mg + 50 mg BD **(Figure 1).**

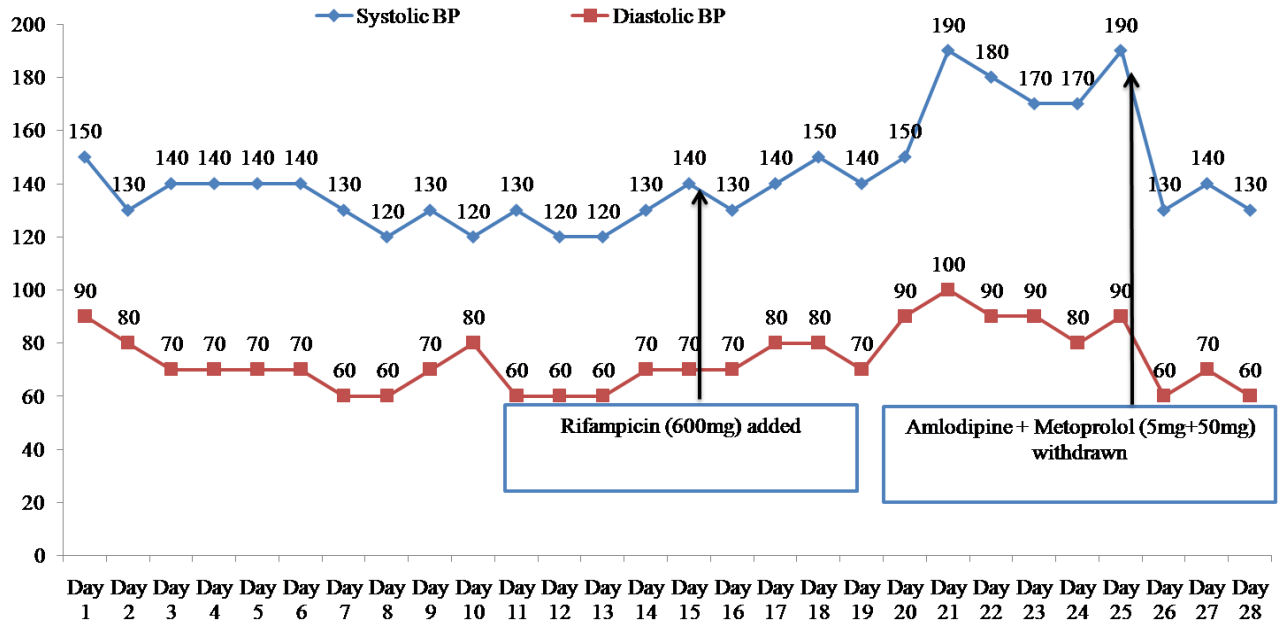


Figure 1: Blood pressure readings before and during anti-tubercular therapy, and after antihypertensive withdrawal

It's interesting to note that the blood pressure measurements gradually improved after the discontinuation of amlodipine and metoprolol. Following the stabilization of blood pressure, the patient felt better, indicating that the de-challenge was successful. With the right guidance, she was qualified for discharge. The patient was advised to return to the hospital for a review and follow-up after one month or sooner if any problems or disease-related symptoms develop.

Discussion

Hypertension control in immunocompromised CKD patients is a major task. For the majority of these individuals, three or more anti-hypertensives at their maximum doses are frequently needed to attain tolerable blood pressure levels. Despite taking multiple drugs in combination, including calcium channel blockers, diuretics, beta-blockers, clonidine, prazosin, and minoxidil, a significant number of CKD patients still have high blood pressure (Duggal *et al.*, 2019).

This case illustrates the major drug-drug interactions between anti-tubercular medication and antihypertensive therapy. After starting rifampicin-based anti-tubercular therapy, the patient's blood pressure regulation was no longer at its ideal level. Similar studies have been reported that emphasized how rifampicin reduced the antihypertensive effects of calcium channel blockers.

In a systematic research to determine whether rifampicin interacts with antihypertensive drugs, Agarwal *et al*. found that patients with CKD exhibited increasing hypertension after starting rifampicin-based anti-tubercular therapy.

Out of 24 CKD patients with worsening hypertension, 84 % required a large increase in antihypertensive medication, and 45 % experienced a hypertensive crisis. Ultimately, rifampicin had to be withdrawn in 9 % of patients to regulate blood pressure (Duggal *et al.*, 2019). Similarly, Soon Leng Lee reported that a 67-year-old man's blood pressure increased after receiving rifampicin as part of his treatment plan for pulmonary tuberculosis. Following six months of anti-tubercular medication, blood pressure levels significantly decreased (Lee *et al.*, 2020).

The most commonly prescribed antihypertensive which is recommended as a first-line medication in hypertensive patients includes dihydropyridine calcium channel blockers. They are known to be a substrate of P450 3A enzymes, specifically CYP3A4, and are primarily metabolized in the liver (Cordeanu *et al.*, 2017) and metoprolol, a lipophilic beta blocker is also metabolized by CYP2D6 in the liver (Lee *et al.*, 2020).On the other hand, Rifampicin, a first-line anti-tubercular medication, is a potent inducer of CYP3A4 in the liver and intestine (Agrawal *et al.*, 2016). When they are administered concomitantly, rifampicin can significantly reduce the plasma levels and therapeutic effects of several CYP3A4 substrates. As a result, there is an increase in the first-pass metabolism of anti-hypertensives, which leads to a decrease in bioavailability and, ultimately, a reduction in the antihypertensive effect (Lee *et al.*, 2020). Therefore, after initiation of rifampicin as part of anti-tubercular therapy, hypertensive CKD patients with previously controlled blood pressure experience worsening hypertension.

Conclusion

The majority of physicians are either unaware of this interaction or generally tend to downplay its clinical significance. As a result, this may significantly raise the morbidity and mortality in this population from hypertension-related causes. After starting rifampicin, a large number of patients from this category end up in the emergency room with a hypertension crisis. Hence, to deal with such clinical situations, there are a few recommendations. Rifampicin should be avoided whenever possible in patients with CKD and hypertension, and rifabutin may be substituted for rifampicin. A thorough blood pressure monitoring regime is necessary if rifampicin is used. This is particularly true in the first two weeks when the induction of liver enzymes is at its highest. Physicians need to become more aware of the clinical importance of rifampicin's interactions with various medications, including frequently prescribed anti-hypertensives. To be widely acknowledged, this interaction needs to be included in anti-tubercular treatment guidelines. Hence it is advised to use extreme caution when prescribing rifampicin-based therapy for hypertensive patients with CKD and prudent monitoring of patients closely for worsening hypertension should be carried out.

Conflict of interest

The authors declare that they have no conflict of interest.

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