

# RIFAMPICIN INDUCED RESISTANT HYPERTENSION IN A PATIENT OF END STAGE KIDNEY DISEASE ON MAINTENANCE HEMODIALYSIS - A CASE REPORT

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## ABSTRACT

Resistant hypertension is common among patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis (MHD) and is usually attributed to volume overload, or inadequate medication adherence. However, drug-drug interactions may be an important and underrecognized cause. We report a 65-year-old man with ESKD secondary to chronic glomerulonephritis, receiving 12 hours a week of MHD, who developed severe refractory hypertension two weeks after initiation of rifampicin-based antitubercular therapy (ATT) for pulmonary tuberculosis. He presented with a blood pressure (BP) of 220/120 mmHg the day after his regular hemodialysis session. Despite prescribing multiple antihypertensive agents in maximum dosages his BP remained persistently elevated even after ruling out volume overload, medication non-adherence, or any renovascular disease. Rifampicin, a potent inducer of hepatic and intestinal cytochrome P450 enzymes, was subsequently discontinued, following which blood pressure gradually improved within three days and normalized to 130/80 mmHg by the tenth day. Thus, rifampicin-induced reduction in the efficacy of antihypertensive medications should always be considered in patients with ESKD who develop abrupt or refractory hypertension after initiation of rifampicin-based ATT.

## KEYWORDS

Drug-drug interaction, end-stage kidney disease, hemodialysis, resistant hypertension, rifampicin

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## INTRODUCTION

Hypertension is a highly prevalent and modifiable risk factor, affecting more than 80.0% of patients undergoing dialysis.<sup>1</sup> It is a major contributor to cardiovascular morbidity and mortality.<sup>2</sup> Although inadequate volume control, increased sympathetic activity, activation of the renin-angiotensin-aldosterone system, arterial stiffness, and medication non-adherence are well-recognized causes of resistant hypertension in this population, drug-drug interactions are often under-recognised causes of it.

Rifampicin has been a cornerstone of first-line antitubercular therapy (ATT) because of its potent bactericidal activity against *Mycobacterium tuberculosis*. It is also a potent inducer of hepatic and intestinal cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6, as well as the drug efflux transporter P-glycoprotein. As a result, rifampicin accelerates the metabolism of many simultaneously administered medications, resulting in reduced plasma concentrations and reduced therapeutic efficacy. Clinically significant interactions have been demonstrated with immunosuppressants, anticoagulants, antiretroviral agents, and several classes of antihypertensive medications, including calcium channel blockers and  $\beta$ -blockers.<sup>3</sup>

End Stage Kidney Disease (ESKD) patients with tuberculosis are increasingly encountered in countries with a high burden of tuberculosis.<sup>5</sup> Patients undergoing maintenance hemodialysis (MHD) are frequently prescribed multiple antihypertensive medications and calcium channel blockers and beta blockers among the first line treatment, placing them at an increased risk of clinically significant pharmacokinetic interactions. Failure to recognize these interactions may lead to refractory hypertension, unnecessary escalation of

antihypertensive medication dosages, frequent hospitalization, and ultimately an increased risk of cardiovascular and cerebrovascular complications.

## CASE REPORT

A 65-year-old man with ESKD secondary to chronic glomerulonephritis, receiving maintenance hemodialysis 12 hours a week, was diagnosed with pulmonary tuberculosis and had been prescribed anti-tubercular therapy (ATT) two weeks before presentation. He presented to the emergency department one day after his scheduled hemodialysis session with severely elevated blood pressure (220mmHg systolic and 120 mmHg diastolic). He also complained of dizziness, headache and blurring of vision. Upon admission, his heart rate was 76 beats/min and respiratory rate was 20 breaths/min.

Fundoscopy examination revealed Grade II hypertensive retinopathy with bilateral papilledema. Cardiovascular examination was mostly unremarkable except concentric left ventricular hypertrophy consistent with his long-term hypertension, while pulmonary examination and imaging revealed with no signs of pulmonary oedema. Ultrasonography study of the abdomen was negative for any evidence of renal artery stenosis. Assessment of medication adherence and compliance to timings of intake confirmed excellent compliance to all his prescribed medications. The patient was anuric since few years, and was receiving adequate hours of maintenance hemodialysis (12 hours/week), consistently achieving his prescribed dry weight, thus making volume overload an unlikely cause of this accelerated hypertension.

He was admitted to the intensive care unit and managed as a case of hypertensive emergency

**Table 1: List of medication given to patient at the time of admission**

| n  | Medication         | Dose                 | Frequency          |
|----|--------------------|----------------------|--------------------|
| 1  | Amlodipine         | 10mg                 | Twice daily        |
| 2  | Metoprolol         | 50 mg                | Once daily         |
| 3  | Prazosin           | 5mg                  | Twice daily        |
| 4  | Clonidine          | 200 mcg              | Thrice daily       |
| 5  | Torsemide          | 100mg                | Twice daily        |
| 6  | Sodium bicarbonate | 500mg                | Twice daily        |
| 7  | Pantoprazole       | 40mg                 | Once daily         |
| 8  | Ferrous sulfate    | 100mg elemental Iron | Twice daily        |
| 9  | Rifampicin         | 450mg                | Once daily         |
| 10 | Isoniazid          | 225mg                | Once daily         |
| 11 | Pyrazinamide       | 1200mg               | Three times a week |
| 12 | Ethambutol         | 800mg                | Three times a week |
| 13 | Pyridoxine         | 40mg                 | Once daily         |

with a continuous intravenous glyceryl trinitrate (GTN) infusion, initiated at 25 µg/min and gradually titrated to achieve controlled blood pressure reduction. Within several hours, his blood pressure decreased to approximately 190/100 mmHg and remained at this level while still on GTN infusion. At the time of admission, his medications included are shown in Table 1.

Despite a continuous GTN infusion, his blood pressure remained elevated at around 210/110 mmHg by third day of admission. Dosages of metoprolol and clonidine were gradually increased to the maximum tolerated dosages with minimal antihypertensive response. The GTN infusion was discontinued on the third hospital day because of persistent throbbing headache and diminishing antihypertensive efficacy, consistent with nitrate tolerance. Given his persistent refractory hypertension, spironolactone was initiated on the seventh hospital day. Regardless of optimization of all his antihypertensive therapy with amlodipine, clonidine, metoprolol, prazosin, and spironolactone at maximally tolerated doses, his blood pressure still remained above 190/100 mmHg after 10 days of intensive treatment.

A comprehensive review of his medications was undertaken. The association between initiation of rifampicin-containing ATT and the onset of accelerated refractory hypertension raised suspicion of a clinically significant drug interaction. Rifampicin is a potent inducer of hepatic cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6, leading to enhanced metabolism and reduced plasma concentrations of several antihypertensive agents, including calcium channel blockers, β-blockers, and α-blockers.

With the suspicion, Rifampicin was discontinued on 12<sup>th</sup> day of hospitalization while the remaining anti-tubercular regimen was continued. A gradual reduction in blood pressure was observed within three days of rifampicin withdrawal without any additional changes to his antihypertensive regimen. By the twentieth hospital day, his blood pressure had normalized to 130/80 mmHg, which strongly urged rifampicin-induced reduction of antihypertensive drug efficacy as the cause of his refractory hypertension.

## DISCUSSION

Refractory hypertension in patients with ESKD receiving maintenance hemodialysis is most of the times of multifactorial cause and commonly results from volume overload, inadequate

dialysis ultrafiltration removal, activation of the renin-angiotensin-aldosterone system, increased sympathetic activity, medication non-adherence, or other secondary causes of hypertension. In this case, all these common etiologies were eventually excluded. The patient was anuric, though receiving adequate thrice-weekly hemodialysis constantly achieving his prescribed dry weight, had good compliance to his antihypertensive medications, and imaging showed no evidence of renovascular disease. The coincidental timeline between the initiation of rifampicin-containing anti-tubercular therapy and the development of accelerated refractory hypertension, followed by gradual normalization of blood pressure after rifampicin withdrawal, strongly supports a clinically significant drug-drug interaction as the underlying mechanism.

Rifampicin is one of the most potent inducers of hepatic and intestinal drug-metabolizing enzymes and transport proteins. It induces cytochrome P450 isoenzymes, particularly CYP3A4 and CYP2D6, as well as P-glycoprotein, resulting in increased metabolism and reduced systemic exposure of numerous medications. Enzyme induction generally begins within several days of treatment initiation, reaches maximal effect within 1–2 weeks, and gradually resolves over approximately 1–2 weeks after discontinuation. The timeline seen in our patient closely mirrors this well-recognized pharmacokinetic profile.

Several antihypertensive agents prescribed to our patient seem susceptible to rifampicin-mediated enzyme induction. Amlodipine a dihydropyridine calcium channel blocker is extensively metabolized by CYP3A4, and concomitant rifampicin administration has been shown to markedly reduce its plasma concentration, leading to loss of antihypertensive efficacy.<sup>4</sup> Metoprolol a selective beta blocker, primarily metabolized through CYP2D6, may exhibit reduced therapeutic activity as well. Although prazosin and clonidine undergo comparatively less cytochrome P450 metabolism, enhanced hepatic metabolism and altered pharmacokinetics have also been reported with rifampicin administration, potentially contributing to reduced blood pressure control.

The management of refractory hypertension in dialysis patients frequently focuses on increasing ultrafiltration, intensifying dialysis, or escalating antihypertensive therapy. However, this case illustrates that pharmacokinetic drug interactions should

always be considered, particularly when hypertension develops abruptly after the introduction of a potent enzyme inducer. Despite maximal tolerated doses of four antihypertensive agents and the addition of spironolactone, our patient's blood pressure remained persistently elevated. Intravenous GTN produced only transient improvement, and its diminishing efficacy was consistent with the development of nitrate tolerance rather than correction of the underlying cause. Recognition of the interaction with rifampicin ultimately led to resolution of the hypertension without requiring further escalation of antihypertensive therapy.

Reports describing rifampicin-induced loss of blood pressure control remain relatively uncommon but have consistently demonstrated substantial reductions in the efficacy of calcium channel blockers and other antihypertensive medications. Case studies show that patients treated for tuberculosis who developed severe hypertension shortly after rifampicin initiation, with restoration of blood pressure control following discontinuation of rifampicin.<sup>5</sup> Our case extends these observations to a particularly vulnerable population of patients with ESKD on maintenance hemodialysis, in whom therapeutic options for resistant hypertension are often limited.

The diagnosis of rifampicin-induced refractory hypertension in this patient was supported by several observations: the relationship between rifampicin initiation and sudden worsening

hypertension, exclusion of other common causes of resistant hypertension, failure to respond to optimization of antihypertensive therapy, and progressive normalization of blood pressure within days of rifampicin withdrawal without major alterations to the remaining treatment regimen. Although rechallenge with rifampicin would have strengthened the causal association, it would have been ethically inappropriate, given the severity of the patient's hypertensive emergency.

This case highlights the importance of performing a comprehensive medication review whenever patients receiving rifampicin develop new-onset or worsening hypertension. Clinicians managing patients with tuberculosis and multiple comorbidities should anticipate clinically significant drug interactions and closely monitor blood pressure during the first few weeks after rifampicin initiation. In patients who develop refractory hypertension despite adequate dialysis and adherence to therapy, consideration should be given to modifying the anti-tubercular regimen where clinically appropriate or selecting antihypertensive agents less susceptible to rifampicin-induced metabolism. Early recognition of this interaction may prevent unnecessary investigations, avoid hospitalization, and ultimately prevent the risk of hypertension-related cardiovascular and cerebrovascular complications.

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