Resistant hypertension during antituberculosis treatment: how is rifampicin implicated?

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SUMMARY

A 67-year-old mental institute resident was treated for smear-positive pulmonary tuberculosis. His background history included chronic essential hypertension which was well-controlled with amlodipine 10mg daily. However, his blood pressure became suboptimal one week into antitubercular treatment, necessitating escalation of antihypertensive therapy up to six medications. Following completion of antitubercular treatment, his blood pressure improved markedly. The number of antihypertensives was able to be reduced to only two after a month. We postulate that rifampicin has attenuated the therapeutic effect of amlodipine via potent induction of hepatic CYP3A4 but the failure to control the blood pressure even with medications unrelated to cytochrome P450 pathways raises the spectre of an additional interaction.

INTRODUCTION

Tuberculosis (TB) is an endemic disease which poses a major health threat globally. On another note, hypertension is a non-communicable disease (NCD) which predisposes to increased risk of cardiovascular disease (CVD). It is not uncommon to encounter patients who harbour both conditions concurrently in Malaysia. These patients require both antitubercular (6 to 12 months) and antihypertensive (long-term) therapies to reduce morbidity and mortality. However, accelerated hypertension during rifampicin-based therapy has been reported in several publications. We report here a case of resistant hypertension which occurred during antitubercular treatment in a previously well-treated hypertensive patient.

CASE REPORT

A 67-year-old mentally challenged man, a long-stay resident in a mental institution, was diagnosed with smear positive pulmonary tuberculosis in April 2019. His background medical problem included chronic essential hypertension which was adequately treated with amlodipine 10mg daily (the recorded blood pressure readings at the institution ranged between 110-135/70-80). The intensive phase of antitubercular therapy consisted of Akurit-4 three tablets daily and pyridoxine 10mg daily was commenced by the respiratory team. Compliance to all medications including antihypertensive was guaranteed by directly observed treatment (DOTS).

One week after starting the antitubercular drugs, his blood pressure control deteriorated with the recorded blood pressure readings ranged from 150-170/85-100mmHg. Gradual escalation of antihypertensive treatment up to six medications including a diuretic at maximum doses (Felodipine 10mg BD, Enalapril 20mg BD, Metoprolol 100mg BD, Prazosin 5mg QID, Methyldopa 1g TDS, Spironolactone 50mg BD), however, failed to achieve satisfactory control throughout his six-month course of antituberculosis treatment (Figure 1). Nevertheless, he suffered no target organ damage.

Clinically, this thin patient (body mass index 16.6kg/m2) had no cushingoid or acromegalic features. Radiological investigations including ultrasound of the kidneys, ureters, and bladder (US KUB) and computed tomography angiography (CTA) of renal arteries ruled out polycystic kidney disease and renal artery stenosis respectively. Echocardiography showed a normal ejection fraction (EF) of 65% with no evidence of coarctation of aorta. Thyroid function test was normal. Screening for phaeochromocytoma was not performed as the patient was taking high doses of methyldopa, the withdrawal of which could risk hypertensive crisis.

Interestingly, following the completion of antitubercular therapy in October 2019, his blood pressure readings dramatically improved, permitting gradual reduction in the number of antihypertensive drugs to only amlodipine 10mg daily and perindopril 4mg daily, one month after (Figure 1). During the last medical review in January 2020, his blood pressure records ranged from 120-140/70-90mmHg while taking these two medications.

DISCUSSION

This case illustrates potential drug-drug interactions between antitubercular therapy and antihypertensive agents, judging by the temporal relationship between the six-month course of tuberculosis treatment and the occurrence of resistant hypertension. The optimal blood pressure control of our patient with only amlodipine 10mg daily (a dihydropyridine calcium channel blocker) was lost with the initiation of rifampicin-based antitubercular therapy. Similar findings have also been reported, that highlighted the attenuation of antihypertensive effects of calcium channel blockers by rifampicin.

Tada Y et al., reported elevated blood pressure during administration of rifampicin as part of the treatment regime for peritoneal tuberculosis which resolved after its discontinuation in a 72-year-old woman who had well-

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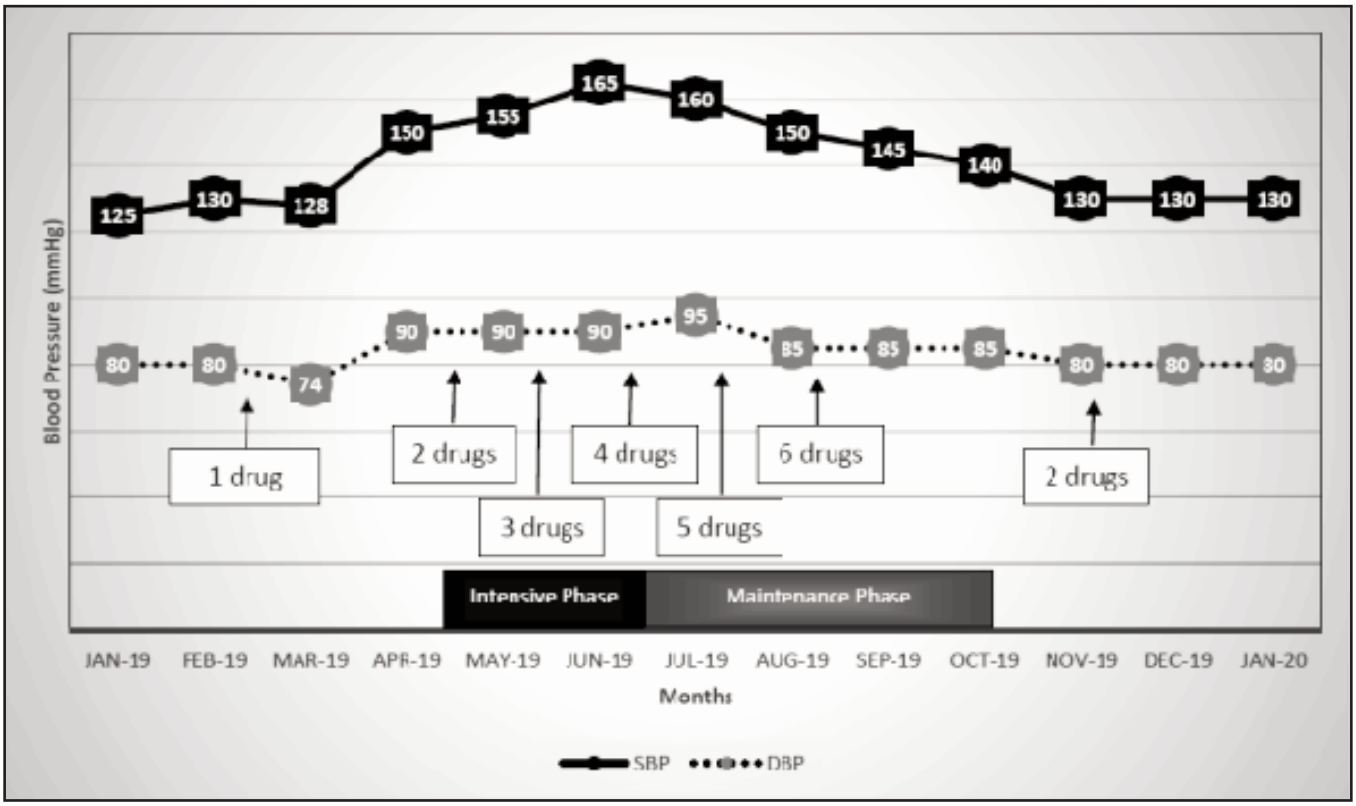

Fig. 1: Serial blood pressure readings before, during and after antitubercular therapy. The time points at which new antihypertensive agents were added successively were indicated by the arrows.

controlled hypertension with nifedipine alone prior. Measurement of plasma concentrations of nifedipine with or without concurrent rifampicin revealed that the peak plasma concentration and the area under the curve were reduced by approximately 60% following administration of rifampicin.[1] Similarly, Cordeanu EM et al., have demonstrated a decrease in the bioavailability of nicardipine when it was co-administered with rifampicin in their patient who developed Posterior Reversible Encephalopathy Syndrome (PRES) due to poorly controlled hypertension which happened in conjunction with the commencement of subcutaneous teicoplanin and oral rifampicin intended for the treatment of septic arthritis.[2]

The reduced bioavailability of calcium channel blocker and therefore its diminished antihypertensive property have been attributed to increased first-pass metabolism of the drug induced by rifampicin. Rifampicin is a strong inducer of cytochrome P450 (CYP) 3A4, both in the liver and the intestine. Hence, it can substantially decrease the plasma levels and therapeutic effects of several CYP 3A4 substrates, among which include verapamil and most dihydropyridine calcium channel antagonists. Full induction of CYP enzymes following initiation of rifampicin is estimated to occur at approximately one week.[3]

Failure to achieve satisfactory blood pressure control with subsequent addition of multiple antihypertensive agents of different classes in our case raises the question of whether rifampicin could be interacting with these agents as well. Metoprolol, a lipophilic beta-blocker, is metabolised by CYP2D6.[4] Decline in plasma concentrations of bisoprolol, metoprolol, propranolol, talinolol and tertatolol has been reported with administration of rifampicin, mediated via induction of CYP2D6.[3] On the other hand, angiotensin-converting enzyme (ACE) inhibitors have not been shown to significantly interact with other drugs through cytochrome P450-mediated metabolism.[4] Similarly, both prazosin (an α1-receptor blocker) and spironolactone (a potassium sparing diuretic) have no known drug interaction via cytochrome P450 pathways.[4] Methyldopa, a central alpha2-adrenergic agonist which reduces sympathetic tone and thus results in a drop in blood pressure, has not been reported to interact with rifampicin.[5] The fact that the blood pressure of our patient remained inadequately controlled with several antihypertensives unrelated to cytochrome P450 pathways puts forth the notion that additional yet-to-be-determined interplays between the drugs or even the diseases could underlie such observation.

The association between arterial hypertension and TB remains unclear. A systematic review of available reports has found no evidence to support such association. However, this finding needs to be interpreted with caution due to the heterogeneity of the studies included as well as the lack of properly designed studies. Aside from the possible direct link between renal TB and kidney damage with resultant hypertension, a potential indirect, immunological link

between TB and hypertension has also been proposed. It is believed that the antibodies produced against the mycobacterial heat-shock proteins (HSP) cross-react with human HSP which are expressed in response to infection by endothelial cells, thus triggering an autoimmune reaction targeting the cells of vessel walls. This in turn leads to dysregulation of blood pressure.[6] It is therefore possible to attribute our conundrum to the said autoimmunity. Nevertheless, no research has been conducted to prove this potential mechanistic link to date.

In conclusion, rifampicin has the potential to diminish hypotensive effects of several antihypertensive agents via cytochrome P450 pathways. Hence, high level of vigilance is recommended when prescribing rifampicin-based treatment for hypertensive patients. Failure to achieve adequate blood pressure control even with medications not known to interact with rifampicin in this case raises the possibility of an additional interaction which is yet to be discerned.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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