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Time course of enzyme induction in rifampicin-warfarin interaction: A case report

Bee Ling Kelly Chng, Jin Shing Hon, Elicia Purnata, Chi Keong Ching

ABSTRACT

Introduction: Concomitant administration of rifampicin and warfarin poses a challenge in achieving stable therapeutic international normalised ratio (INR). There is no published case report in Singapore to show the time course for enzyme induction and de-induction in Asian patient. Case Report: A 90-year-old man was on a stable warfarin dose of 1.5 mg daily for stroke prevention in atrial fibrillation with therapeutic INR before switching to rivaroxaban and subsequently apixaban. He was initiated with a 9-month course of rifampicin, isoniazid, pyridoxine and ethambutol for treatment of pulmonary tuberculosis. Hence, apixaban was switched back to warfarin. Therapeutic INR was first achieved 20 days after a dose increment of 166% in warfarin from 1.5 mg daily to 4 mg daily. The INR subsequently decreased again and warfarin dose was increased to 4.5 mg daily. A 2-fold increment in warfarin dose was required to reach the second therapeutic INR at week-7. INR was stable in therapeutic range with 4.5 mg daily and patient was followed up every 2 to 4 weeks. Time in therapeutic range (TTR) was 74% over the course of nine months. After five days of discontinuing rifampicin, INR decreased to 1.70 despite maintaining the same dose of warfarin. Conclusion: The total time course of enzyme induction takes about six to seven weeks to reach a steady state. The de-induction of enzyme may not occur within the first week of rifampicin discontinuation. Close INR monitoring during the initial phase of initiation or termination of rifampicin is required.

Keywords: Enzyme induction, Interaction, Rifampicin, Time Course, Warfarin

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INTRODUCTION

The World Health Organization (WHO) reported that Tuberculosis (TB) remains one of the major public health concerns in the South-East Asia Region with steadily increasing TB cases [1]. Rifampicin is one of the widely used first-line drugs for the treatment of tuberculosis and commonly used to treat other infections such as meningitis, osteomyelitis and endocarditis besides tuberculosis [2]. However, rifampicin can induce multiple enzymes responsible for drug metabolism such as cytochrome P450 (CYP) 2C9, CYP 3A4, CYP 2C19, CYP 1A2, other detoxification pathways and several drug transporters like P-glycoprotein [3]. Direct oral anticoagulants such as apixaban and rivaroxaban are metabolized via CYP 3A4. Therefore, rifampicin use is contra-indicated in patients on rivaroxaban and apixaban because it increases metabolism of rivaroxaban and apixaban, reducing their anticoagulation efficacy and puts patient at higher risk of thromboembolic events.

Although warfarin is also metabolized via CYP 2C9 and CYP 3A4, it can be used together with rifampicin with appropriate dosage titration to achieve therapeutic international normalised ratio (INR). Therefore warfarin remains the drug of choice for patient with atrial fibrillation and requiring rifampicin. Several case reports showed challenges and difficulty to achieve therapeutic INR when rifampicin was co-administered with warfarin [4–8]. In addition, there is no published case report in Singapore to show the time course for enzyme induction and de-induction in Asian patient.

This case report demonstrates the dosage increment required and time course for enzyme induction between warfarin and rifampicin in a patient with atrial fibrillation who developed tuberculosis.

CASE REPORT

A 90-year-old Chinese man with a history of hypertension, hyperlipidaemia, ischaemic heart disease, atrial myxoma, paroxysmal atrial fibrillation, transient ischaemic attack, chronic kidney disease and gout was on a stable warfarin dose of 1.5 mg per day. Patient's INR reading was within therapeutic INR range (2.0 to 3.0) for two years. Warfarin was switched to rivaroxaban 15 mg daily on 15 April 2015 and subsequently replaced by apixaban 2.5 mg twice daily on 1 December 2016 when his renal function deteriorate during inpatient admission as apixaban is less renally cleared. His concurrent medications were apixaban 2.5 mg twice daily, bisoprolol 5 mg daily, valsartan 80 mg daily, simvastatin 20 mg at night and colchicine 500 mcg twice daily when necessary.

He developed pulmonary tuberculosis (PTB) on 15 December 2016 and was given rifampicin 600 mg daily, isoniazid 300 mg daily, pyridoxine 20 mg daily and ethambutol 1000 mg three times a week. Rifampicin can reduce blood concentration of apixaban that may reduce effectiveness of apixaban for stroke prevention [9]. Therefore, apixaban was switched to warfarin with a plan to up-titrate warfarin dose weekly until his INR is therapeutic.

As shown in Table 1, patient was loaded with warfarin 2 mg once daily for three days on 16 December 2016. Patient was then continued on 1.5 mg once daily for two days. He remained sub-therapeutic with INR 1.20 despite warfarin dose increment for three weeks. Therefore, a different approach using larger dose increment with closer monitoring every three to four days was chosen. INR increased from 1.20 to 2.10 in four days after dose was increased to 4 mg daily (87% daily dose increment). Due to this drastic increased in INR, warfarin dose was decreased to 3 mg once daily. INR decreased to 1.80 after three days and dose was then increased to 3.5 mg per day for four days. Even though INR was 1.90 after four days, the same dose was maintained. Subsequently, patient's INR decreased to 1.50. Hence, patient was loaded with one dose of warfarin 5 mg and then up-titrated to 4.5 mg

Table 1: Summary of warfarin dose titration

Day	Previous warfarin dose	INR	Warfarin dose changes	% dose change
Day 5	2 mg daily for three days from 16 December 2016 (Day 1); then 1.5 mg daily for two days	1.60	2 mg daily	+33%
Day 14	2 mg daily	1.20	2 mg 5 times/ week; 2.5 mg 2 times/ week	+7%
Day 21	2 mg 5 times/ week; 2.5 mg 2 times/week	1.20	4 mg daily	+87%
Day 25	4 mg daily	2.10	3 mg daily	-25%
Day 28	3 mg daily	1.80	3.5 mg daily	+17%
Day 32	3.5 mg daily	1.90	Same	0%
Day 38	3.5 mg daily	1.50	5 mg for 1 day; 4.5 mg daily	+29%
Day 41	4.5 mg daily	1.90	Same	0%
Day 49	4.5 mg daily	2.40	Same	0%
Day 56	4.5 mg daily	2.50	Same	0%
Day 70	4.5 mg daily	2.00	Same	0%
Day 98	4.5 mg daily	2.10	Same	0%
Day 124	4.5 mg daily	1.98	4 mg 3 times/ week; 5 mg 4 times/ week	+1.6%
Day 153	4 mg 3 times/ week; 5 mg 4 times/week	2.10	Same	0%
Day 209	4 mg 3 times/ week; 5 mg 4 times/week	2.30	Same	0%
Day 264	4 mg 3 times/ week; 5 mg 4 times/week	1.92	Same	0%
Day 278	4 mg 3 times/ week; 5 mg 4 times/week	1.70	Warfarin stopped and replaced with rivaroxaban 15 mg daily. Rifampicin (15 December 2016 to 15 September 2017) was stopped at day-273.	

daily for three days. Therapeutic INR was finally achieved in week-7 with warfarin dose of 4.5 mg daily, a two-fold increment of warfarin dose. There was a slight increment of warfarin dose (1.6%) when INR dropped to 1.98 at day-124.

After concomitant administration of rifampicin and warfarin, therapeutic INR was first achieved in 20 days (Figure 1). When INR became subtherapeutic after that, it took another 24 days to reach therapeutic range (Figure 1). Time in therapeutic range (TTR) was 74% over the 9-month course.

Rifampicin was discontinued on day-273. After 5 days of rifampicin discontinuation, INR dropped to 1.70 despite patient taking the same dosage of warfarin. The INR trend post rifampicin cessation was not stipulated in detail because warfarin was switched to rivaroxaban 15 mg daily five days after rifampicin was stopped.

Patient was compliant to the medications throughout the nine months course of concomitant rifampicin and warfarin. There were no changes in the lifestyle or medications.His liver function and renal function were stable.

DISCUSSION

It is challenging to predict a patient's response to warfarin and the dosage adjustment required when pulmonary tuberculosis medications especially rifampicin is initiated or discontinued. There are few studies publishing the magnitude of dosage adjustment required when there is drug-drug interaction involving rifampicin and warfarin and majority of the studies showed challenges in anticoagulation management [4–8].

Martins et al (2013) described a 59-year-old Brazilian woman treated with warfarin for stroke prevention in atrial fibrillation requiring a three months sequential increases of warfarin dosage from 45 mg per week to 80 mg per week to reach therapeutic INR. Warfarin dosage had to be doubled at the beginning of rifampicin therapy [10].

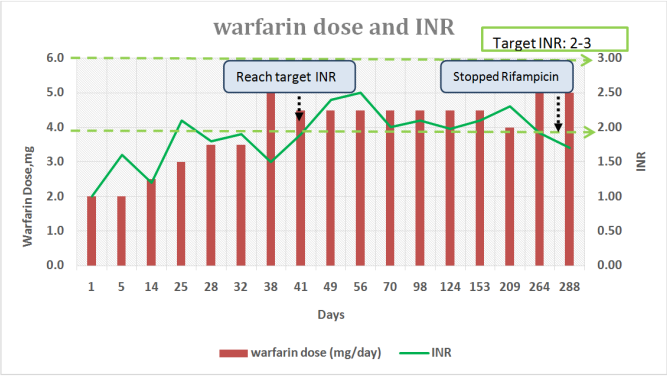

Figure 1: Warfarin dose and INR during concomitant administration of rifampicin and warfarin.

Our case report showed that therapeutic INR can be achieved within a shorter period of seven weeks with frequent INR monitoring every three to four days and a higher dosage adjustment. A 200% of dose increment was required to attain therapeutic INR over seven weeks.

INR reducing from 1.90 to 1.50 with the same warfarin dosage of 3.5 mg daily on the 5th week of concomitant rifampicin and warfarin suggested the possibility of rifampicin inducing enzymes in a gradual pattern by phases. Our finding estimated that the time course of induction most likely reach a steady state by week-7 of concomitant interacting drugs administration. Although rifampicin has a half-life elimination of about 3 to 4 hours, the time required to produce maximum enzyme induction is much longer because of the requirement of producing additional enzymes [3].

We expected to see an up-trending of INR after stopping rifampicin, but in contrast, we observed a drop in INR to 1.70 despite continuing the same dosage of warfarin. This indicates that a dose reduction of warfarin may not be required within the first week of stopping rifampicin but frequent INR monitoring is required. Jessica Dawson (2016) also reported a drop of INR from 2.50 to 1.50 with empirically dose reduction of 14% (from 35 mg per day to 30 mg per day) after five days discontinuation of rifampicin [11].

The time course of de-induction remains complex and poorly understood. The de-induction of the enzymes may happen gradually when the enzyme-inducing drug is stopped. The de-induction of hepatic enzymes not only depends on elimination of the inducing agent but also the natural degradation time of the enzymes [3].

Meanwhile, we suggest a higher dosage increment with close INR monitoring in three to five days during the co-administration of warfarin and rifampicin so that therapeutic INR can be achieved within shorter period of time. We were unable to observe the INR trend after rifampicin was stopped as warfarin was switched to rivaroxaban subsequently. Should the patient be continued on warfarin after the completion of rifampicin, every three to seven days monitoring of INR for the first four weeks of rifampicin discontinuation is recommended to prevent incidence of thromboembolic events and bleeding complications.

CONCLUSION

Rifampicin induces enzymes gradually by phases. The total time course of enzyme induction takes about six to seven weeks to reach a steady state. Immediate warfarin dose reduction is not necessary as the de-induction of enzyme may not occur within the first week of discontinuation. Close INR monitoring during the initial phase of initiation or termination of rifampicin is required. Further studies can be conducted to investigate

the prolonged onset and offset of interactions so that the interaction duration can be better predicted.

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Author Contributions

Bee Ling Kelly Chng – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Jin Shing Hon – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Elicia Purnata – Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Chi Keong Ching – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.