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Decreased serum voriconazole levels caused by hepatic enzyme induction after rifapentine discontinuation: a case report and literature review

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Abstract. – BACKGROUND: Rifapentine is a rifamycin with unique bactericidal activity against *Mycobacterium tuberculosis*. It is also a potent inducer of CYP3A activity. However, the duration of rifapentine-induced hepatic enzyme activity after withdrawal is unclear.

CASE REPORT: We report a case of a patient with *Aspergillus* meningitis treated with voriconazole after discontinuing rifapentine. Within ten days of rifapentine discontinuation, serum levels of voriconazole failed to reach the effective treatment range.

CONCLUSIONS: Rifapentine is a potent inducer of hepatic microsomal enzymes. The induction of hepatic enzymes may exceed ten days after rifapentine discontinuation. Clinicians should be reminded of residual enzyme induction by rifapentine, especially when treating critically ill patients.

Key Words:
Rifapentine, Hepatic enzyme induction, Voriconazole, Duration.

Introduction

Rifapentine is a rifamycin antibiotic similar in structure and activity to rifampicin and rifabutin. It is combined with other agents to treat tuberculosis, particularly in once- or twice-weekly regimens[1-4]. Although rifapentine has a similar antibacterial activity to rifampicin, its minimum inhibitory concentration (MIC) is two-to-four times lower than that of rifampicin[5,6]. Rifapentine is slowly absorbed after oral administration, with a bioavailability of 70% and a half-life of 13.2 hours[7]. A study reported that the peak concentration (C_{max}) of rifapentine is more significant than that of rifampicin and rifabutin at the commonly used dosage[8]. Aristoff et al[9] found that the C_{max} of rifapentine was 15.0 mg/L, the protein binding rate was 97.0%, and the C_{max}/MIC ratio for evaluating the bactericidal effect was 375, under the weekly dose of 600 mg. Furthermore, rifapentine retains a prolonged post-antibiotic effect similar to rifampicin, and the antibacterial effect can continue for up to 75 hours after exposure to *Mycobacterium tuberculosis*[7].

Rifapentine is mainly metabolized to 25-diacetyl rifampicin in the liver, however, it also been found an inducer of the hepatic microsomal cytochrome P450 (CYP) enzyme[5,6,10]. The rifamycins induce enzyme systems involved in the metabolism of many drugs, most notably those metabolized by CYP 3A. However, there are few studies on hepatic enzyme induction by rifapentine or the duration of the induction effect[11,12].

Voriconazole is a triazole and is the first-line treatment for invasive aspergillosis. Therapeutic drug monitoring of voriconazole has become the standard of care to ensure efficacy and avoid adverse effects[13,14]. Low serum voriconazole concentrations are associated with treatment failure, which may have devastating consequences in severely ill individuals. Voriconazole is metabolized by CYP[15]. Therefore, combining drugs that induce hepatic enzymes may lead to decreased serum voriconazole levels. Here, we report a case of *Aspergillus* meningitis treated with voriconazole that did not reach the effective therapeutic concentration after rifapentine discontinuation.

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Case Presentation

An 85-year-old man (height: 165 cm; weight: 35 kg) was transferred from another hospital and diagnosed with pulmonary tuberculosis and *Aspergillus* meningitis. The patient had a history of rifapentine use on March 11, 2022 (oral administration, 450 mg, twice a week) for treating pulmonary tuberculosis with *Aspergillus* meningitis. On March 19, 2022, the patient was transferred to our hospital's tuberculosis intensive care unit (ICU) for further treatment. Upon admission, the patient was in a coma and critical condition due to the intracranial infection.

The patient was treated with voriconazole (150 mg every 12 hours) for *Aspergillus* meningitis on the first day of admission. Because rifapentine induces hepatic enzymes, it was not given to the patient (the final administration of rifapentine was on March 18). To ensure the efficacy and safety of voriconazole, serum levels were monitored. The serum trough concentration (C_{trough}) was first monitored after reaching a stable pharmacokinetic state on March 21, 2022 (three days after rifapentine withdrawal). The result was 0.55 μg/ml, lower than the effective concentration range (1.0-5.0 μg/ml). After consultation with the clinical pharmacist, the voriconazole dose was adjusted, considering the possibility of enzyme induction after rifapentine discontinuation. Thus, with the clinician's consent, the dosage was changed from 150 mg to 200 mg every 12 hours. The second monitoring was conducted on March 23, 2022 (five days after rifapentine discontinuation). The C_{trough} was < 0.5 μg/ml (below the lower limit of quantification), much lower than the effective concentration. Therefore, the dosage interval was decreased to 200 mg every eight hours. The third C_{trough} was drawn on March 28, 2022 (ten days after rifapentine discontinuation). The serum voriconazole level was 1.81 μg/ml, within the effective concentration range (1.0-5.0 μg/ml). The changes in serum voriconazole level during the treatment are shown in Figure 1. To prevent liver function injury caused by voriconazole, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were also monitored. During treatment, the ALT and AST levels increased, and AST levels exceeded the normal range from March 23 to 27 (Figure 2), suggesting that liver function might be impaired. However, the patient's family discontinued treatment for economic reasons. The patient was discharged from the hospital on April 1, 2022, 14 days after admission.

Voriconazole is recommended for adults weighing less than 40 kg to be given at a loading dose (200 mg every 12 hours) within the first 24 hours, followed by a maintenance dose of 100 mg twice daily. In our case, the dosage (150 mg every 12 hours) exceeded the maintenance dose of the instruction, considering enzyme induction by rifapentine. However, the serum voriconazole levels failed to reach the effective treatment range within ten days of rifapentine discontinuation.

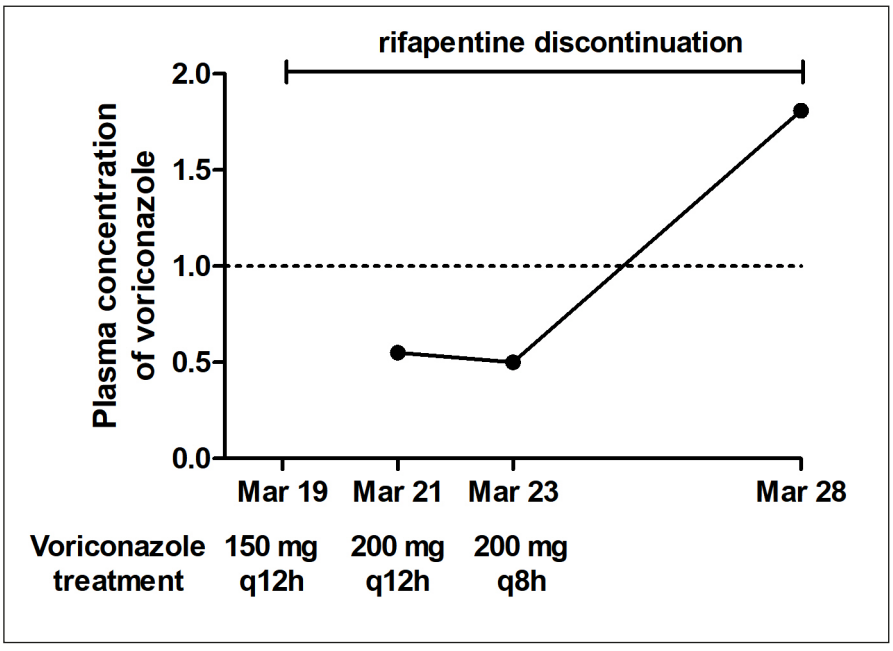

Figure 1. Changes in serum voriconazole levels during treatment. The dashed line indicates the lower limit of the effective range of voriconazole.

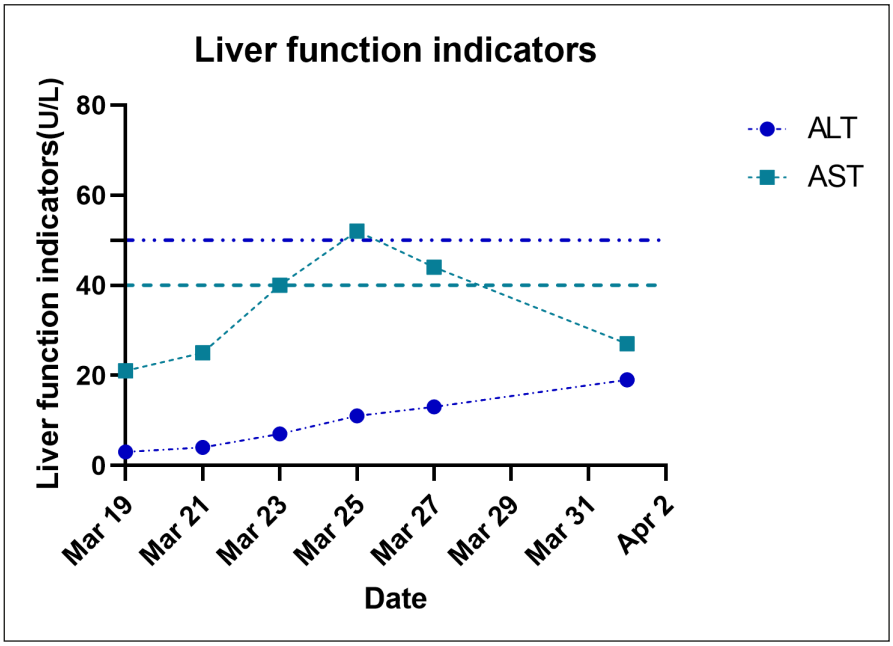

Figure 2. Changes of liver function indicators during the voriconazole treatment. The dashed lines represent the upper limits of normal ranges for ALT and AST.

Discussion

This case report is the first instance of serum voriconazole levels failing to reach the therapeutic range ten days after discontinuing rifapentine for treating *Aspergillus* meningitis. This finding suggests that the duration of rifapentine's induction effect on hepatic enzymes may exceed ten days and reminds clinicians to be aware of the residual enzyme induction effect of rifapentine, especially when treating critically ill patients.

In this case, the following issues were considered: (1) the mechanism of enzyme induction effect by rifapentine; (2) the strength of enzyme induction by rifapentine; and (3) the duration of enzyme induction after rifapentine discontinuation. Burman et al[6] and Niemi et al[12] proposed that rifapentine might mediate the induction of hepatic microsomal CYP3A4 through a human orphan nuclear receptor (Pregnane X Receptor, PXR) similar to rifampicin. PXR binds to response elements in the CYP3A4 promoter and is activated by several agents (including rifampicin), enhancing CYP3A4 protein synthesis[16]. The specific mechanism is illustrated in Figure 3. Li et al[17] determined that the order of the induced activity of CYP3A4 by rifamycin was rifampicin > rifapentine > rifabutin by measuring the liver microsomal CYP3A4 enzyme activity using indirect testosterone 6β-hydroxylation. Williamson et al[18] and Dooley et al[19] proposed a new order of the induced activity (rifampicin > rifabutin > rifapentine) based on *in vitro* polymerase chain reaction and revealed that rifapentine had a more substantial CYP3A4 induction effect than rifampicin when combining rifampicin or rifapentine with midazolam (a typical CYP3A4 probe drug). An *in vitro* study from Japan[20] found that CYP3A4 induction by rifapentine was more robust than rifampicin at 10 μM in human hepatoma cells. These findings suggest that additional studies are needed to study the strength of the enzyme induction effect by rifapentine.

In the present case, liver function was slightly impaired during voriconazole treatment, which theoretically reduced the drug metabolism by hepatic enzymes. However, the drug level of voriconazole remained below normal, which indirectly indicated the induction effect of rifapentine. Vital Durand et al[21] also studied the induction effect of rifapentine on hepatic microsomal enzyme and found that rifapentine (600 mg/48 h) for ten days in six healthy volunteers resulted in a significant reduction in the half-life of antipyrine, with a corresponding increase in total clearance; these values returned to normal ranges after rifapentine discontinuation for 12 days. Another study[22] revealed that the increase of hepatic microsomal enzyme activity induced by rifapentine might occur within four days after taking the first dose and that this activity would return to the baseline range after rifapentine discontinuation for 14 days. These results suggest that the duration of rifapentine's induction effect on hepatic enzymes may be 12-14 days.

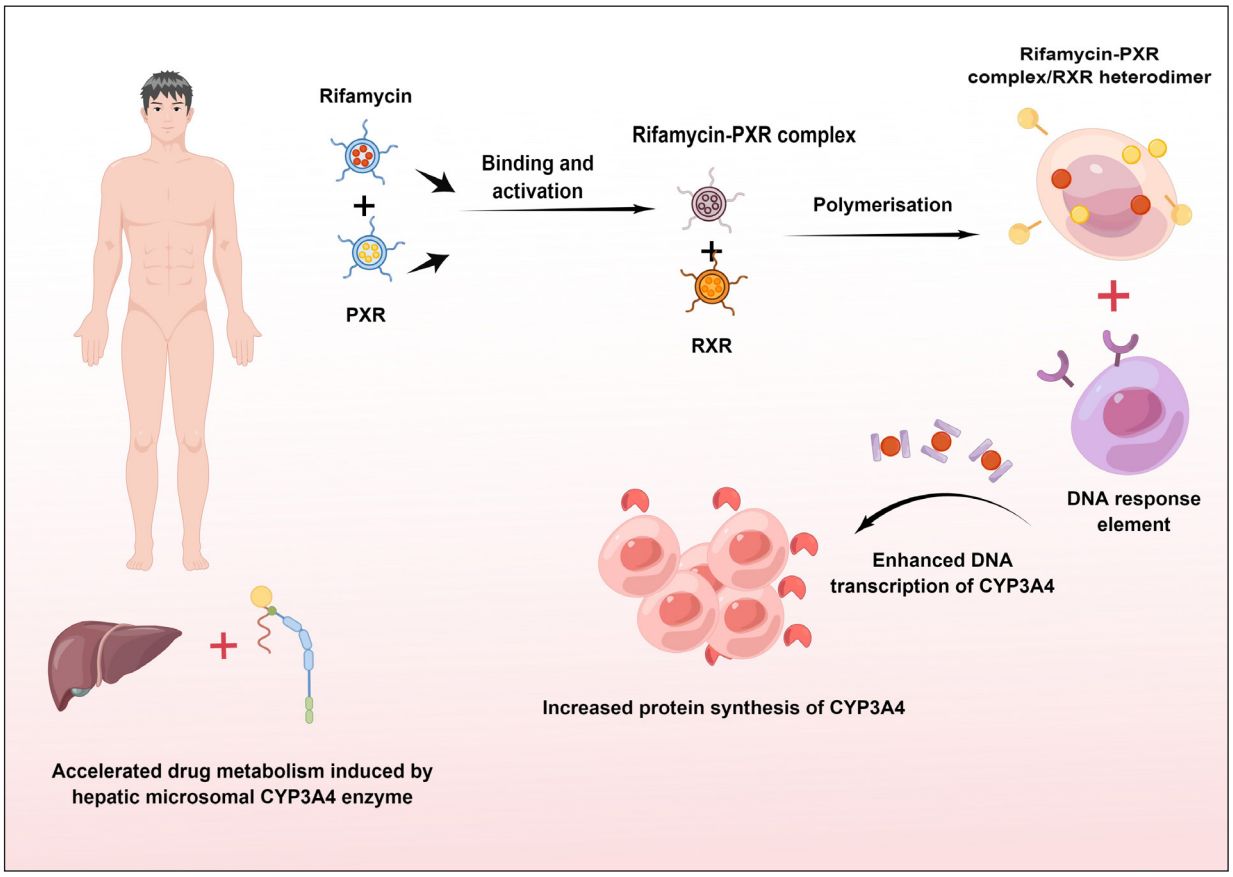

Figure 3. Mechanism of rifamycin-mediated induction of hepatic microsomal CYP3A4. PXR: pregnane X receptor. RXR: retinoid X receptor.

In our case report, the C_{trough} of voriconazole was above the lower effective concentration limit only after ten days of rifapentine discontinuation when the dose was far greater than the recommended dose. This finding suggests that the residual time of hepatic enzyme induction after rifapentine discontinuation may exceed ten days. The family members discontinued treatment for economic reasons, which resulted in the failure to monitor the therapeutic agents during follow-up; nevertheless, we believe that an accurate definition of the residual time of rifapentine-mediated hepatic microsomal enzyme induction will be achieved with in-depth exploration in more clinical cases in the future.

Conclusions

Rifapentine is a potent inducer of hepatic microsomal enzymes, and the duration of induction on hepatic enzymes may exceed ten days after rifapentine discontinuation. Therefore, given the widespread use of rifapentine, clinicians should be aware of the residual enzyme induction effect, especially when treating critically ill patients.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Written consent was obtained from the patient.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions

G.-M. Ling drafted the manuscript; J.-M. Li and Y.-P. Jing performed the data processing and statistical analyses; X.-J. Cai and R.-Y. Zhang helped draft the manuscript. All authors approved the final version.

References

1) Munsiff SS, Kambili C, Ahuja SD. Rifapentine for the treatment of pulmonary tuberculosis. Clin Infect Dis 2006; 43: 1468-1475.
2) Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006. Rifapentine 2022; 24: 15-39.
3) Alfarisi O, Alghamdi WA, Al-Shaer MH, Dooley KE, Peloquin CA. Rifampin vs. rifapentine: what is the preferred rifamycin for tuberculosis? Expert Rev Clin Pharmacol 2017; 10: 1027-1036.
4) van Ingen J, Aarnoutse RE, Donald PR, Diacon AH, Dawson R, Plemper van Balen G, Gillespie SH, Boeree MJ. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? Clin Infect Dis 2011; 52: e194-e199.
5) Chan JG, Bai X, Traini D. An update on the use of rifapentine for tuberculosis therapy. Expert Opin Drug Deliv 2014; 11: 421-431.
6) Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet 2001; 40: 327-341.
7) Jarvis B, Lamb HM. Rifapentine. Drugs 1998; 56: 607-616.
8) Birmingham AT, Coleman AJ, Orme ML, Park BK, Pearson NJ, Short AH, Southgate PJ. Antibacterial activity in serum and urine following oral administration in man of DL473 (a cyclopentyl derivative of rifampicin). Br J Clin Pharmacol 1978; 6: 455P-456P.
9) Aristoff PA, Garcia GA, Kirchhoff PD, Showalter HD. Rifamycins-obstacles and opportunities. Tuberculosis (Edinb) 2010; 90: 94-118.
10) Sirgel FA, Fourie PB, Donald PR, Padayatchi N, Rustomjee R, Levin J, Roscigno G, Norman J, McIlleron H, Mitchison DA. The early bactericidal activities of rifampin and rifapentine in pulmonary tuberculosis. Am J Respir Crit Care Med 2005; 172: 128-135.
11) Dooley K, Flexner C, Hackman J, Peloquin CA, Nuermberger E, Chaisson RE, Dorman SE. Repeated administration of high-dose intermittent rifapentine reduces rifapentine and moxifloxacin serum levels. Antimicrob Agents Chemother 2008; 52: 4037-4042.
12) Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 2003; 42: 819-850.
13) Moriyama B, Kadri S, Henning SA, Danner RL, Walsh TJ, Penzak SR. Therapeutic Drug Monitoring and Genotypic Screening in the Clinical Use of Voriconazole. Curr Fungal Infect Rep 2015; 9: 74-87.
14) Job KM, Olson J, Stockmann C, Constance JE, Enioutina EY, Rower JE, Linakis MW, Balch AH, Yu T, Liu X, Thorell EA, Sherwin CM. Pharmacodynamic studies of voriconazole: informing the clinical management of invasive fungal infections. Expert Rev Anti Infect Ther 2016; 14: 731-746.
15) He HR, Sun JY, Ren XD, Wang TT, Zhai YJ, Chen SY, Dong YL, Lu J. Effects of CYP3A4 polymorphisms on the serum level of voriconazole. Eur J Clin Microbiol Infect Dis 2015; 34: 811-819.
16) Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest 1998; 102: 1016-1023.
17) Li AP, Reith MK, Rasmussen A, Gorski JC, Hall SD, Xu L, Kaminski DL, Cheng LK. Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: evaluation of rifampin, rifapentine and rifabutin. Chem Biol Interact 1997; 107: 17-30.
18) Williamson B, Dooley KE, Zhang Y, Back DJ, Owen A. Induction of influx and efflux transporters and cytochrome P450 3A4 in primary human hepatocytes by rifampin, rifabutin, and rifapentine. Antimicrob Agents Chemother 2013; 57: 6366-6369.
19) Dooley KE, Bliven-Sizemore EE, Weiner M, Lu Y, Nuermberger EL, Hubbard WC, Fuchs EJ, Melia MT, Burman WJ, Dorman SE. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. Clin Pharmacol Ther 2012; 91: 881-888.
20) Nakajima A, Fukami T, Kobayashi Y, Watanabe A, Nakajima M, Yokoi T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: rifampicin, rifabutin, and rifapentine. Biochem Pharmacol 2011; 82: 1747-1756.
21) Vital Durand D, Hampden C, Boobis AR, Park BK, Davies DS. Induction of mixed function oxidase activity in man by rifapentine (MDL473), a long-acting rifamycin derivative. Br J Clin Pharmacol 1986; 21: 1-7.
22) Zheng C, Hu X, Zhao L, Hu M, Gao F. Clinical and pharmacological hallmarks of rifapentine's use in diabetes patients with active and latent tuberculosis: do we know enough? Drug Des Devel Ther 2017; 11: 2957-2968.