Infection and Drug Resistance

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ORIGINAL RESEARCH

The Effect of Rifapentine and Rifampicin on Serum Voriconazole Levels Persist for 5 Days and 7 Days or More After Discontinuation in Tuberculosis Patients with Chronic Pulmonary Aspergillosis

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Purpose: Voriconazole, a first-line therapeutic agent for chronic pulmonary aspergillosis, is metabolized by the cytochrome 450 enzymes, specifically CYP2C19 and CYP3A4. Rifampicin and rifapentine act as inducers of the cytochrome P450 enzyme. The current study explored the potential drug interactions arising from the co-administration of voriconazole with either rifampicin or rifapentine, as well as the duration of this effect on serum voriconazole levels after discontinuation of rifampicin or rifapentine.

Patients and Methods: A retrospective study was conducted in tuberculosis patients with chronic pulmonary aspergillosis. These patients underwent a combination therapy involving voriconazole and rifampicin or rifapentine, or they were treated with voriconazole after discontinuation of rifampicin or rifapentine. The serum concentrations of voriconazole at steady-state were monitored. Data on demographic characteristics and the serum voriconazole levels were used for statistical analyses.

Results: A total of 124 serum voriconazole concentrations from 109 patients were included in the study. The average serum concentration of voriconazole fell below the effective therapeutic range in patients treated with both voriconazole and rifampicin or rifapentine. Notably the co-administration of rifapentine led to a substantial (>70%) decrease in serum voriconazole levels in two patients. Moreover, this interfering effect persisted for at least 7 days following rifampicin discontinuation, while it endured for 5 days or more after discontinuation of rifapentine.

Conclusion: Concomitant use of voriconazole and rifampicin or rifapentine should be avoided, and it is not recommended to initiate voriconazole therapy within 5 or 7 days after discontinuation of rifapentine or rifampicin. Therapeutic drug monitoring not only provides a basis for the adjustment of clinical dose, but also serves as a valuable tool for identifying drug interactions.

Keywords: voriconazole, rifampicin, rifapentine, serum concentration, discontinuation

Introduction

Tuberculosis (TB) poses a serious threat to global health, ranking as the leading cause of death from a single infectious agent since in 2014. According to the global TB report 2023, 7.5 million people worldwide were newly diagnosed with TB in 2022, marking the highest figure since WHO began global TB monitoring in 1995.[1] China continues to grapple with a high burden of TB. Even worse, TB is a significant risk factor for fungal infection, as cavitary lesions post TB infection can provide good reservoirs for fungal colonization.[2] Chronic pulmonary aspergillosis (CPA), a destructive pulmonary disease caused by *Aspergillus* species, was estimated to affect approximately 1.2 million people in the world as a sequel to TB.[3] Persistent respiratory symptoms associated with CPA are observed in about 20% of patients after two months of intensive anti-TB treatment.[4] Voriconazole (VOR) is recommended as the first-line long-term treatment for

Received: 29 January 2024
Accepted: 24 June 2024
Published: 8 July 2024

Aspergillus, and its serum concentration at a steady state is monitored to evaluate the efficacy and safety of the treatment.[5,6] But it has been found that a few *Aspergillus* isolates were resistant to azoles, which correlates with poor therapeutic outcome of zole. The studies indicated that nonsynonymous mutations in the cyp51A and overexpression of mdr1 and mfs genes resulted in azole-resistant phenotypes of *Aspergillus*.[7,8] VOR is metabolized in the liver via the cytochrome P-450 (CYP450) enzyme family, which is mainly metabolized by CYP2C19 and CYP3A4, with CYP2C9 involvement being minimal. As a result, inducers or inhibitors of CYP2C19 and CYP3A4 and genotype status of CYP2C19 may give rise to variations in the serum concentration of voriconazole.[9–11] A number of studies have demonstrated a relationship between VOR plasma concentration and clinical efficacy and toxicity, and the rate of treatment success was associated with VOR trough concentration of >0.5 mg/L.[12–14] Therefore therapeutic drug monitoring (TDM) of VOR is important to improve the treatment response and reduce adverse events.[15,16]

Rifampicin (RFP) is a first-line drug for the treatment of drug-susceptible TB. RFP is a potent inducer of both the hepatic and intestinal CYP-450 enzyme system and P-glycoprotein (P-gp) transport system.[17] Rifapentine (RFT) is a semi-synthetic rifamycin derivative from the piperazinyl hydrazone class with a microbiologic profile similar to that of RFP, which induces CYP-450 enzyme less than RFP, but RFT has a longer-duration action than RFP.[18] In our hospital, treatment with RFT is substituted when patients have adverse drug reactions suspected to be caused by RFP. The medication package insert for VOR (Zyvox™; Pfizer Pharmaceuticals, New York, NY, USA) states that administration of VOR with RFP results in 93% and 96% reduction in the peak serum concentration (C_{max}) and area under the drug concentration-time curve (AUC) for VOR, respectively, hence VOR combination with RFP is forbidden. Moreover concomitant administration of VOR with rifabutin results in 69% and 78% reduction in the C_{max} and AUC of VOR, respectively. But the effect of RFT on serum VOR level is not mentioned in the package insert for VOR. Research concerning the drug interaction between VOR and RFT is rare. When the serum concentration of VOR can reach the therapeutic range after discontinuation of RFP or RFT was unclear.

The objective of the present study was to investigate the effect of combination of RFP or RFT on VOR serum concentration, and the duration of effect on VOR serum trough concentration after discontinuation of RFP or RFT in TB patients with CPA.

Patients and Methods

Patients

This single retrospective study included TB patients with CPA who were admitted at the TB Diagnosis and Treatment Center of Affiliated Changsha Central Hospital, the University of South China and who underwent therapeutic drug monitoring (TDM) of VOR trough concentration (C_{min}) from April 2016 to July 2023. The study was approved by the Ethics Committee of the Affiliated Changsha Central Hospital (2020103).

The inclusion criteria were patients: (1) aged ≥18 years; (2) receiving continuous VOR at a maintenance dose of 200 mg per body every 12 h (Q12h) for treatment >5 days; (3) for whom TDM results of VOR at steady state were available; (4) who were treated by co-administration of VOR with RFP or RFT; (5) who were treated with VOR after discontinuation of RFP or RFT.

The exclusion criteria were patients: (1) who were pregnant or lactating; (2) who were administered other drugs that strongly reduced VOR serum concentration (eg carbamazepine, phenytoin, phenobarbital, rifabutin, efavirenz, ritonavir, St. John's wort) simultaneously; (3) undergoing blood purification or other forms of kidney-replacement therapy. The flow chart of the study procedure is shown in Figure 1.

Determination of VOR Serum Concentration

When VOR had reached a steady-state concentration (after at least 4 days), blood was collected 30 min before the next administration to monitor the C_{min}. VOR serum concentrations were analyzed by high-performance liquid chromatography using a photodiode array (HPLC-PDA, Shimadzu LC-20AT). The analytical method met the requirements for determination of biological samples, with absolute recovery >90% and a linear range of 0.12–20.64 mg/L ($R^2 = 0.9997$). The limit of quantification was 0.12 mg/L, and values that were below this level were recorded as 0. The intra-day

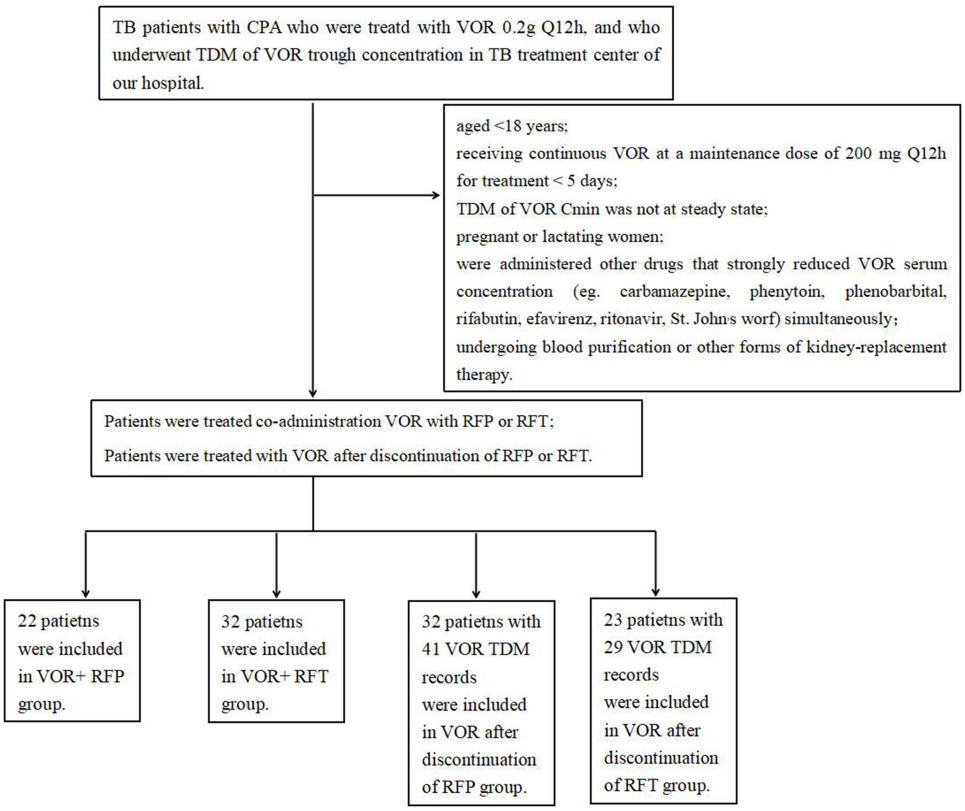

Figure 1 The flow chart of study procedure.

precision and inter-day precision were <5%. The C_{min} of VOR in the range 1.0–5.5 mg/L was considered to be in the therapeutic range.[19]

Data Collection

The electronic medical record system (EMRS) of ACCH was used to retrieve and collect patient information. The data collected were organized as: (1) demographics (age, sex); (2) detection time and results of VOR C_{min}; (3) laboratory data for liver function (albumin, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase) and renal function (creatinine, urea nitrogen); and (4) the presence or absence of co-medication with proton pump inhibitor (PPI).

Statistical Analysis

Continuous variables are presented as the mean ± SD according to the normality (Kolmogorov–Smirnov) test. To estimate differences between variables, the chi-square test and Student´s *t*-test were used for categorical variables and continuous parametric variables, respectively. Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, Inc., San Diego, USA). The *P*-value <0.05 was statistically significant.

Results

Demographic Characteristics of the Patients

A total of 109 TB patients with CPA for whom VOR serum concentrations were monitored, amounting to 124 measured concentrations, were included in the study: 22 patients were in VOR + RFP group, and 32 patients were in VOR + RFT group; 32 patients were in after discontinuation of RFP group, while 23 patients were in after discontinuation of RFT group. The serum concentration of VOR was monitored twice in 11 patients, and VOR C_{min} was monitored three times in 2 cases. A total of 100 patients were treated with VOR injection, 8 patients used VOR tablets, and 1 case used tablets for

Table 1 Characteristics of Patients in the Two Groups

	VOR+RFP Group (*n* = 22)	VOR+RFT Group (*n* = 32)	P	After RFP Discontinuation (*n* = 32)	After RFT Discontinuation (*n* = 23)	P
Age, years	57.95 ± 11.38	64.04 ± 16.99	0.147	52.44 ± 18.54	66.30 ± 15.19	0.005**
Sex (Male/Female)	20 / 2	25 / 7	0.821	26/6	15/8	0.770
Albumin, g/L	31.36 ± 5.34	32.84 ± 5.78	0.347	31.44 ± 6.82	31.49 ± 6.23	0.978
TBIL, μmol/L	7.03 ± 3.32	8.26 ± 3.32	0.187	7.04 ± 4.71	7.24 ± 4.07	0.870
DBIL, μmol/L	4.56 ± 3.22	4.98 ± 2.18	0.571	3.88 ± 4.09	4.03 ± 2.67	0.877
ALT, U/L	14.16 ± 9.25	15.15 ± 11.56	0.740	20.58 ± 19.78	12.60 ± 6.52	0.068
AST, U/L	27.80 ± 17.07	24.40 ± 10.60	0.370	34.37 ± 26.59	33.46 ± 35.57	0.914
Creatinine, μmol/L	50.68 ± 13.34	61.25 ± 26.80	0.094	55.02 ± 19.79	79.70 ± 95.82	0.161
UN, mmol/L	4.23 ± 1.55	5.72 ± 4.19	0.118	6.58 ± 9.34	8.83 ± 10.19	0.400
Co-treatment with PPI *N* (%)	6 (27.27)	5 (15.62)	0.896	2 (6.25)	7 (30.43)	0.221

Abbreviations:TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UN, urea nitrogen; PPI, proton pump inhibitor.

three days then changed to injection. A total of 50 patients were treated with RFP 450 mg every day (qd), 3 patients with 600 mg qd, and 1 case with 300 mg qd. Forty-eight patients were administered with RFT 450 mg twice a week (biw), 3 cases with 600 mg biw, 3 cases with 300 mg biw, and 1 case with 750 mg biw. RFP or RFT was taken in the morning on an empty stomach. All patients took bland diet in hospitalization. The characteristics of patients are displayed in Table 1. Except for patient age between after discontinuation of RFP/RFT groups, there were no significant differences in the basic characteristics of patients.

Serum Concentrations of VOR in Co-Administration with RFP or RFT

The serum concentrations of VOR were lower than the therapeutic range in all 22 patients who received VOR + RFP, with 68.18% (15/22) exhibiting serum VOR concentrations below the quantification limit of 0.12 mg/L. In contrast, serum VOR levels within the reference range of 1.00 to 5.50 mg/L were observed in 6 patients who received VOR + RFT, although 21.88% (7/32) of VOR C_{min} was under the limit of quantification of 0.12 mg/L. As shown in Figure 2, the

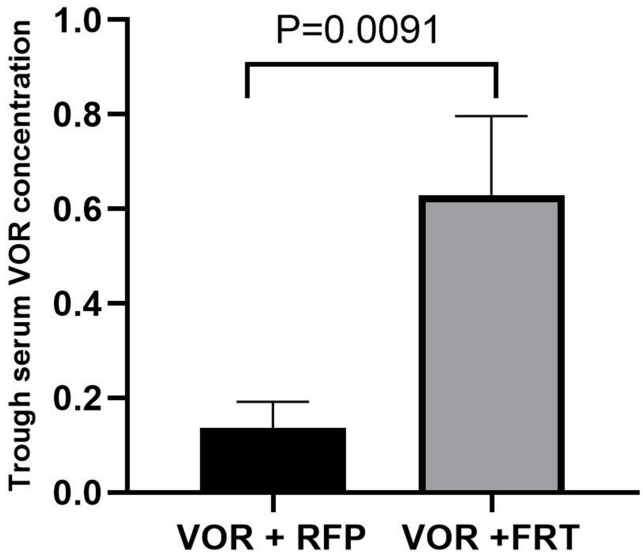

Figure 2 VOR Cmin in patients who had co-administration with RFP or RFT.

mean value of serum VOR concentration was significantly lower in patients who received VOR with RFP (0.14 ± 0.26 mg/L) than in those who received VOR with RFT (0.63 ± 0.97 mg/L).

The drug interaction between RFT and VOR is not mentioned in the medication package insert for VOR (Pfizer Pharmaceuticals, New York, NY, USA). The serum VOR concentrations of two patients who were treated with VOR injection for 7 days and 5 days were 1.38 mg/L and 2.52 mg/L, respectively, while they decreased to 0.25 mg/L and 0.72 mg/L after co-administration with RFT for 10 days and 7 days, respectively, which suggested that the serum concentration of VOR reduced by 71.4%–81.9% when VOR was combined with RFT.

Recovery of the Serum VOR Concentration After Discontinuation of RFP

A total of 32 patients, contributing to 41 VOR TDM records, were included to investigate the recovery of serum VOR concentration after discontinuation of RFP. The results were categorized into three different time periods following RFP discontinuation: 1–3 days (n=12), 4–6 days (n=20), and more than 7 days (n=9). The mean C_{min} of VOR were 0.36 ± 0.34 mg/L and 0.49 ± 0.56 mg/L during the periods of 1–3 days and 4–6 days after RFP discontinuation. As shown in Figure 3, the average C_{min} of VOR measured ≥7 days after discontinuation of RFP was 1.34 ± 0.72 mg/L, significantly higher than those measured during 1–3 days and 4–6 days after RFP discontinuation (P<0.05). The distribution of serum VOR concentration after RFP discontinuation is displayed in Table 2.

Repeat measurements were carried out for 8 patients in whom serum VOR concentrations were lower than 1.0 mg/L after RFP discontinuation within 5 days. Apart from the eighth patient in whom the serum VOR levels were 0.72 mg/L and 0.91 mg/L on day 7 and day 10 after discontinuation of RFP, the VOR concentrations in the remaining 7 patients clearly increased to the target range after discontinuation of RFP for more than 6 days. Detailed results are displayed in Table 3.

Recovery of the Serum VOR Concentration After Discontinuation of RFT

A total of 23 patients, yielding 29 VOR TDM records, were included to assess the recovery of serum VOR concentration following the discontinuation of RFT. The time intervals were defined as 1–3 days (n=9), 4–5 days (n=12), and more than 6 days (n=8) after RFT discontinuation. The average C_{min} of VOR were 0.45 ± 0.41 mg/L and 0.49 ± 0.33 mg/L during 1–3 days and 4–5 days after RFT discontinuation. As shown in Figure 4, the mean C_{min} of VOR measured ≥6 days after

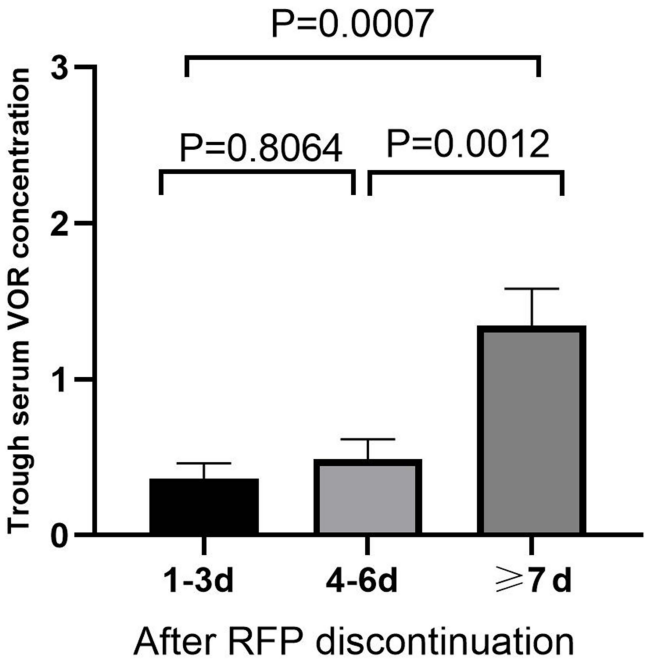

Figure 3 VOR Cmin in patients after RFP discontinuation.

Table 2 Distribution of VOR Cmin After RFP Discontinuation

VOR Cmin (mg/L)	After Discontinuation of RFP (N/%)		
	1–3 days	4–6 days	≥ 7 days
<0.12	4 (9.76%)	5 (12.19%)	0
0.12–1.0	8 (19.51%)	12 (29.27%)	3 (7.32%)
1.0–5.5	0	3 (7.32%)	6 (14.63%)
Total	12 (29.27%)	20 (48.78%)	9 (21.95%)

Table 3 Several VOR TDM After Discontinuation of RFP in 8 Patients

Patient No.	Sex	Age (years)	The First TDM / (mg/L)	Time of the First TDM (Days after RFP Discontinuation / d)	The Second TDM / (mg/L)	Time of the Second TDM (Days after RFP Discontinuation / d)
1	Male	26	0.18	3	1.38	7
2	Male	53	0.49	5	1.74	7
3	Male	64	0	2	2.19	6
4	Male	69	0.60	1	2.14	7
5	Female	47	0.32	1	1.12	6
6	Female	30	0.37	4	1.15	11
7	Male	77	0	2	1.58	6
8	Female	66	0.37	5	0.91	10

RFT discontinuation was 2.31 ± 0.91 mg/L, significantly higher than those measured during 1–5 days after discontinuation of RFT (P<0.0001). The distribution of VOR C_{min} after RFT discontinuation is displayed in Table 4.

The serum concentrations of VOR were repeatedly measured in 5 patients after RFT discontinuation. As shown in Table 5, the VOR concentrations remained below 1.0 mg/L in 4 patients within the initial 4 days after RFT

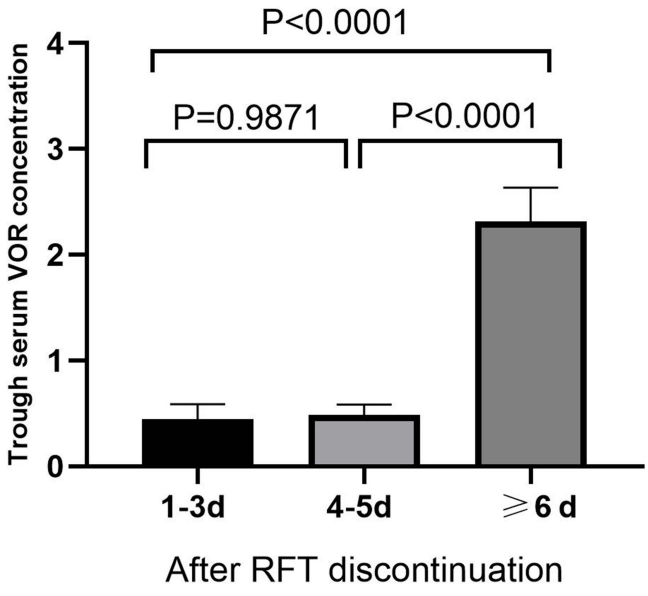

Figure 4 VOR Cmin in patients after RFT discontinuation.

Table 4 Distribution of VOR Cmin After RFT Discontinuation

VOR Cmin (mg/L)	After Discontinuation of RFT (N/%)		
	1–3 days	4–5 days	≥ 6 days
<0.12	3 (10.34%)	2 (6.90%)	0
0.12–1.0	5 (17.24%)	10 (34.48%)	0
1.0–5.5	1 (3.45%)	0	8 (27.59%)
Total	9 (31.03%)	12 (41.38%)	8 (27.59%)

Table 5 Several VOR TDM After Discontinuation of RFT in 5 Patients

Patient No.	Sex	Age (years)	The First TDM / (mg/L)	Time of the First TDM (Days after RFT Discontinuation / d)	The Second TDM / (mg/L)	Time of the Second TDM (Days after RFT Discontinuation / d)
1	Male	75	0.50	2	2.01	8
2	Male	82	0.31	2	1.69	6
3	Male	78	1.09	2	1.83	6
4	Male	55	0.29	4	2.04	7
5	Male	77	0.35	4	2.69	10

discontinuation, but exhibited a notable increase beyond 6 days. The serum VOR concentrations in all patients reached the target range from the sixth day after RFT discontinuation.

Discussion

Previous experiments have revealed that VOR undergoes transformation into N-oxide and is metabolized by liver CYP2C19, CYP3A4, and CYP2C9 enzymes,[10] and thus drugs that inhibit or induce these activities probably affect the serum concentration of VOR. RFP is an inducer of CYP-450 oxidative enzymes, including CYP3A4, CYP2C19, CYP2C9, CYP1A2, and CYP2D6.[17,20] Consequently, the combination of VOR and RFP leads to a loss of the therapeutic efficacy of VOR due to the underexposure. The C_{max} of VOR and AUC in one patient was 3.92 mg/L and 27.4 h mg/L after the starting dose (400 mg), but the VOR exposure was decreased by 99% after 36 days of VOR therapy and 30 days of RFP therapy, with a C_{max} of 0.038 mg/L and an AUC of 0.145 h mg/L. Meanwhile the plasma concentrations of three main metabolites were similar or even increased compared to the concentrations following the first dose without RFP.[21] Co-administration of RFP was associated with a significant reduction in VOR exposure.[13,22] Research has indicated that the total apparent clearances increased twofold in CYP2C9 activity, irrespective of the CYP2C9 genotypes in healthy volunteers after RFP administration.[23] The average serum concentrations of VOR in all 22 patients co-administered with RFP was only 0.14 mg/L in the present study, which is consistent with the effect of RFP on serum itraconazole levels.[24]

RFT induces CYP3A4 and CYP2C8/9 as shown in human hepatocyte study,[25] but the relative enzyme induction of RFT is less potent than that of RFP.[20] Studies about the drug interaction with RFT are rare,[26] and RFT was not included in clinically significant drug interactions with VOR.[27,28] Therefore RFT is commonly substituted for RFP in order to minimize the drug interaction between VOR with RFP in the hospital. A serum concentration of VOR in the target range of 1.0–5.5 mg/L was only achieved in 18.75% of measurements in patients who were treated combination with VOR and RFT in the study. The average serum VOR concentration in the VOR + RFT group was 0.66 mg/L, lower than the therapeutic range, but was significantly higher than that in the VOR + RFP group. The serum concentrations of VOR in two patients reduced by more than 70% after administration with RFT. Previous study reported that the steady-state serum C_{max} and AUC of indinavir were decreased by 55% and 70%, respectively,[18] which was consistent with the present study.

Enzyme induction activity and the pharmacodynamic effects of the affected drug gradually return to baseline levels within 9–14 days after discontinuation of RFP.[29,30] Studies about duration of effect of RFP on serum VOR concentration after discontinuation of RFP therapy were scarce. One case reported that the inductive effect of RFP on plasma VOR concentration was notable for at least 13 days in a 32-year-old patient with invasive central nervous system aspergillus.[31] In our study a total of 9 C_{min} measurements of VOR were in the therapeutic range of 1.0–5.5 mg/L after RFP discontinuation. Only 9.38% (3/32) patients' serum VOR level reached the target range after discontinuation of RFP for 6 days, but the percentage of VOR C_{min} >1.0 mg/L was 66.67% (6/9) after RFP discontinuation for 7 days or more. Meanwhile the serum VOR levels in 8 repeated monitoring patients were gradually increased. RFT is approved for intermittent dosing in the treatment of TB, with a serum half-life several times higher than RFP.[32] However the duration of induced enzyme activity after discontinuation of RFT is unclear. Enzyme activity of RFT returns to baseline within 2 weeks after the last dose of RFT.[33] The serum concentrations of VOR failed to reach the effective treatment range in an 85-year-old man within 10 days of RFT discontinuation, which suggested the induction of hepatic enzymes may exceed 10 days after stopping RFT.[34] There were 9 serum concentrations of VOR that reached the target range after RFT discontinuation in the present study, but all serum VOR concentrations measured ≥6 days after discontinuation of RFT were in the therapeutic range. As the elimination half-life of RFT is 14.8 h to 18.5 h,[26] the effect of RFT on the serum concentration of VOR receded markedly after discontinuation for 5 days. Except for the enzyme-induced activity, the difference of effect duration on serum VOR concentrations after discontinuation of RFP or RFT may be related to the age of patients. In the present study, the median age of the patients in the after RFT discontinuation group was 69 (range 34–93), and 69.56% were >60 years of age. In addition, the age of patients in the after discontinuation of RFT group was markedly older than the age of patients in the after RFP discontinuation group. The previous studies had demonstrated the relationship between patient age with serum level of VOR, and the VOR concentrations in patients older than 60 years were higher than in younger patients.[35,36] In older patients, the hepatic drug clearance is decreased, and the apparent volume of distribution of lipophilic drugs (such as VOR) is increased with a prolonged half-life.[37] Although VOR is regarded as the first-line drug for the treatment of *Aspergillus*, its use is limited in TB patients by a wide range of drug interactions, especially rifamycin. Therefore, consideration should be given to starting with liposomal amphotericin B (L-AmB) or echinocandins with close monitoring of liver and kidney function to avoid this significant drug interaction. Once the patient is ready for discharge, oral VOR or isavuconazole may be used as maintenance therapy.[38–41]

There are a few limitations in this study. The serum concentration of VOR is lower than the effective range when VOR is combined with RFT, and the question remains whether doubling the dose of VOR to 400 mg Q12h would make the steady-state plasma VOR concentration reach the target range. As CYP2C19 gene variants had been well established to influence the VOR pharmacokinetics, we should assess the gene polymorphisms in the future research. This is a single-center study, and we will utilize a larger study cohort to confirm the finding.

Conclusion

The present study demonstrated that the serum concentrations of VOR were lower than the effective treatment range when combined with RFP or RFT. The average C_{min} of VOR in VOR + RFT patients was significantly higher than the mean value of VOR in VOR + RFP group. The serum VOR levels were decreased by more than 70% when combined with RFT. Concomitant use of RFT and VOR should be avoided. The duration of inductive effect on serum VOR concentration was at least 7 days after RFP discontinuation, while it lasted for 5 days or longer after discontinuation of RFT. VOR TDM is an important tool for identifying the drug interactions of clinical significance and to improve the treatment response in TB patients with CPA.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of the Affiliated Changsha Central Hospital, the University of South China (approval number 2020103). This study complied with the Declaration of Helsinki. Waiving of informed consent was given due to the retrospective, observational study. All patient data were collected anonymously and ensured the confidentiality of their information.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, analysis of data; took part in drafting the article or revising it critically for important content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Hunan Medical Association of China with a fund number [MHA202001007].

Disclosure

The authors report no conflicts of interest in this work.

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