Received: 24 March 2021 | Revised: 2 June 2021 | Accepted: 4 June 2021

DOI: 10.1111/bcp.14953

LETTER TO THE EDITOR

Challenge in treating COVID-19 associate pulmonary aspergillosis: Supratherapeutic voriconazole levels

Sir,

There is a cumulative evidence suggesting COVID-19 victims are prone to COVID-19 associated pulmonary aspergillosis (CAPA). COVID-19 itself and immunomodulatory medications, such as corticosteroids and tocilizumab, compromise the immune system to an extent that opportunistic infections complicate the course further.[1] In this letter, we aimed to highlight the relationship between inflammation and voriconazole trough levels in COVID-19 patients.

Voriconazole is recommended as the first-line agent for the treatment of invasive pulmonary aspergillosis (IPA).[1] Voriconazole is metabolized with cytochrome P450 (CYP450) isoenzymes (mainly with CYP2C19 and lesser extent with CYP3A4) to voriconazole N-oxide. Voriconazole reaches to steady-state trough concentrations approximately at the fifth day of administration. Therapeutic drug monitoring for voriconazole is recommended because of the narrow therapeutic index.[2] Voriconazole dose for IPA is recommended as 4 mg/kg every 12 h for maintenance, followed by 6 mg/kg loading dose every 12 h in the first day. It was recommended that the trough level of voriconazole should be between 1.5 and 5.5 mg/L. Voriconazole trough level over 4.5–6 mg/L has been associated with hepatotoxicity.[3] The common side effects of voriconazole were defined as visual disturbances, fever, nausea, rash, vomiting, chills, headache, abnormal liver function tests, and hallucinations.[4]

Since the beginning of COVID-19 pandemic, a total of 13 COVID-19 patients were treated with voriconazole for CAPA in our university hospital based on mycological, clinical, and radiological findings. Among 13 patients, 12 (92.3%) were critically ill. All patients, except one, had bacterial or viral coinfection in addition to CAPA. Plasma voriconazole level measurements were performed with liquid chromatography-triple quadrupole mass spectrometer (Shimadzu LCMS-8040). Two of those had a DDI with voriconazole (with 500-mg intravenous clarithromycin twice daily and 80-mg oral omeprazole daily), which might contribute to high voriconazole trough levels due to their inhibitory effect on CYP450 isoenzymes. However, the voriconazole level remained elevated despite discontinuation of clarithromycin in one patient, suggesting a different mechanism. In five (41.7%) critically ill patients, the trough level of voriconazole remained in the supratherapeutic range despite a dose reduction of 100 mg/day. In summary, no associated factor was detected for the explanation of higher voriconazole trough levels in 12 critically ill patients. It was observed that COVID-19 patients were more prone to high voriconazole levels than non-COVID-19 patients. In four of 13 non-COVID-19 patients, the voriconazole trough level was supratherapeutic. COVID-19 and non-COVID-19 patients were comparable in terms of gender (46.2% vs. 46.2%, $p = 1.000$), age [median (inter quartile range): 63 (51.5–69.5) vs. 66 (46.5–72.0) years, $p = .960$] and the number of comorbidities [median (inter quartile range): 2 (1–3.5) vs. 3 (1–4), $p = .724$]. Fatality was 69.2% versus 61.5% among COVID19 and non-COVID19 patients, respectively ($p = .680$). Since most of our patients were hospitalized in the intensive care unit, we were only able to monitor increased transaminase levels, which is one of the common findings of voriconazole toxicity. Transaminases levels were significantly higher in patients with COVID-19 (53.8% vs. 7.7%, $p = .030$). There was no significant difference in the first CRP levels between the groups [median (inter quartile range): 11.20 (6.84–15.19) vs. 7.78 (3.99–10.43), $p = .153$]. Voriconazole levels were also significantly higher in the COVID-19 group [median (inter quartile range): 5.8 (4.75–6.75) vs. 2.4 (0.99–4.60), $p = .001$]. A mild and positive correlation was determined between trough levels of voriconazole and C reactive protein (CRP) levels ($r = 0.443$, $p < .001$) (Figure 1).

For example, in a 57-year-old female patient (patient #11), despite the therapeutic voriconazole level on day 6, an approximately twofold increase was measured on 20th day of the treatment. Even though voriconazole dose was reduced to 100 mg per day, its trough concentration was in 9.0 mg/L) on day 27. Therapeutic voriconazole trough level range could be achieved 5 days after discontinuation of the treatment. A relation between voriconazole trough levels and simultaneous (CRP) levels was observed in the patient and no other explanatory reason for supratherapeutic levels of voriconazole was found (Table 1).

Pharmacokinetics of voriconazole is affected by many factors such as impaired liver functions, drug–drug interactions (DDIs), bodyweight of the patient, genetic polymorphism, and food intake in oral use. Regardless, inflammatory cytokines may inhibit the activity of enzymes by causing downregulation of CYP450 isoenzymes. Van Wanrooy et al. previously reported higher voriconazole trough levels in patients with higher CRP values. Voriconazole trough levels were elevated 0.015 mg/L for each 1 mg/L increase in CRP level.[5] Although the possible mechanism of inflammatory cytokines on cytochrome P450 isoenzymes is not clear, microRNA (miRNA) molecules may play a role in the regulation of gene expression. In general, binding of miRNA molecules and small noncoding RNAs to recognition sites on target mRNA, leads to inhibition of the translation and transcription pathways of gene expression. It was observed that levels of miRNA-21 and miRNA-130b were increased during inflammation.[6]

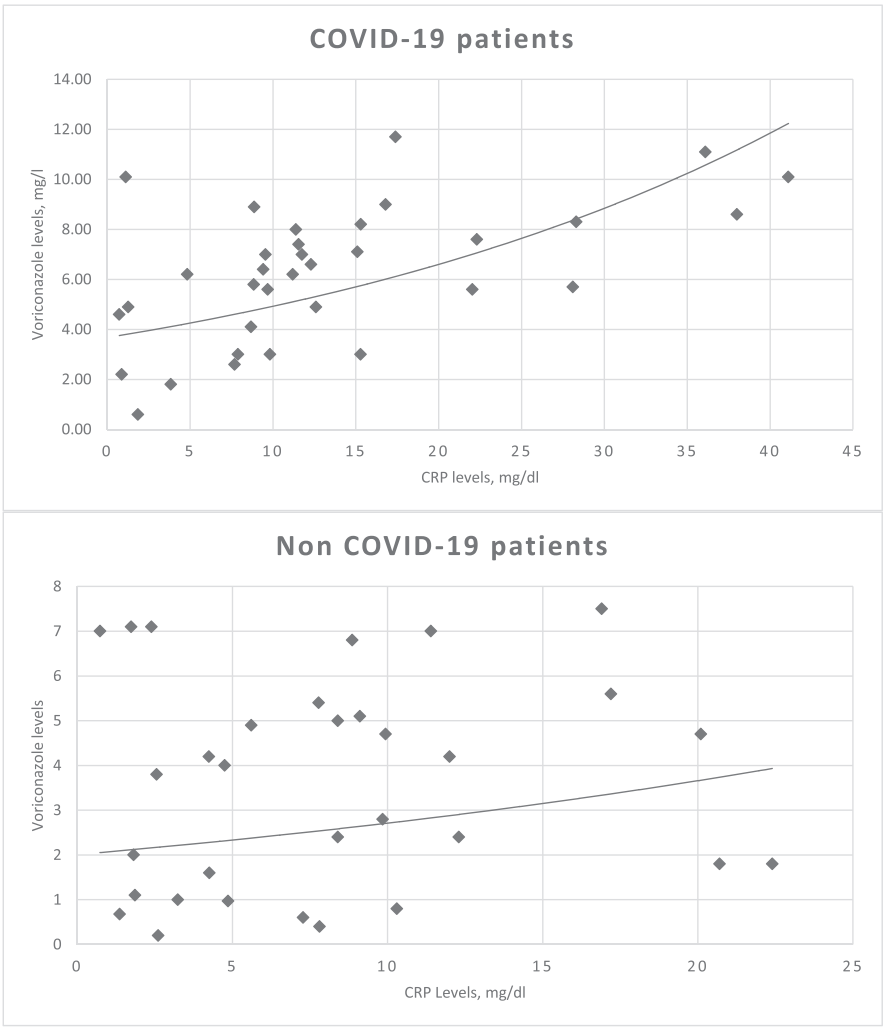

FIGURE 1 The relationships of voriconazole and CRP levels in COVID-19 and non COVID-19 patients

TABLE 1 Disease and treatment characteristics of patients and voriconazole, and CRP levels

COVID-19 patients							
Patient #	**Characteristics of patients**	**Weight (kg)**	**Voriconazole dosage**	**Route**	**Level and day of voriconazole[a]**	**CRP (mg/dl)**	**The day of COVID-19 when CAPA is diagnosed**
1	67 years, male (critically ill)	80	320 mg q12h (2 × 480 mg loading)	iv	4.6 mg/L (6th day)	0.73	20th
					8.2 mg/L (11th day)	15.30	
2	77 years, male (critically ill)	60	200 mg q12h (2 × 300 mg loading)	iv	7.1 mg/L (5th day)	15.10	11th
					5.6 mg/dl (6th day)	9.68	
					7.0 mg/dl (11th day)	11.75	
3	78 years, male (critically ill)	70	280 mg q12h (2 × 420 mg loading)	iv	7.4 mg/dl (5th day)	11.55	38th
			200 mg q12h		11.7 mg/dl (9th day)	17.40	
					2.2 mg/dl (5th day)	0.87	
4	64 years, female (critically ill)	75	300 mg q12h (2 × 500 mg loading)	iv	5.8 mg/dl (6th day)	8.85	21st
5	70 years, female (critically ill)	80	320 mg q12h (2 × 480 mg loading)	iv	6.2 mg/dl (4th day)	4.83	15th

TABLE 1 (Continued)

COVID-19 patients							
Patient #	**Characteristics of patients**	**Weight (kg)**	**Voriconazole dosage**	**Route**	**Level and day of voriconazole[a]**	**CRP (mg/dl)**	**The day of COVID-19 when CAPA is diagnosed**
6	55 years, male (non-critically ill)	65	200 mg q8h (2 × 400 mg loading)	po	4.9 mg/dl (5th day)	12.60	26th
					0.6 mg/dl (48th day)	1.86	
			300 mg q12h	iv	3.0 mg/dl (55th day)	7.89	
					10.1 mg/dl (63rd day)	1.12	
7	40 years, female (critically ill)	65	260 mg q12h (2 × 390 mg loading)	iv	5.6 mg/dl (8th day)	22.03	19th
			210 mg q12h	iv	8.6 mg/dl (13th day)	38.00	
			Drug stopped				
8	63 years, female (critically ill)	70	280 mg q12h (2 × 420 mg loading)	iv	6.4 mg/dl (4th day)	9.42	13th
			250 mg q12h	iv	7.0 mg/dl (10th day)	9.55	
9	61 years, female (critically ill)	75	360 mg q12h	iv	6.2 mg/dl (7th day)	11.20	9th
			300 mg q12h	iv	8.3 mg/dl (14th day)	28.30	
			200 mg q8h	po			
			Drug stopped		1.8 mg/dl (20th day)	3.84	
10	69 years, male (critically ill)	75	200 mg q8h (2 × 450 mg iv loading)	po	4.9 mg/dl (6th day)	1.27	23rd
					5.7 mg/dl (12th day)	28.10	
11	57 years, female (critically ill)	73	290 mg q12h (2 × 430 mg loading)	iv	3.0 mg/dl (6th day)	9.820	13th
					6.6 mg/dl (20th day)	12.30	
			240 mg q12h	iv	9.0 mg/dl (27th day)	16.80	
			Drug stopped		10.1 mg/dl (28th day)	41.10	
					8.9 mg/dl (29th day)	8.87	
					1.9 mg/dl (33rd day)	20.20	
12	48 years, male (critically ill)	70	280 mg q12h (2 × 420 mg loading)	iv	7.6 mg/dl (6th day)	22.30	18th
					11.1 mg/dl (11th day)	36.10	
			Drug stopped				
13	43 years, male (critically ill)	90	360 mg q12h (2 × 540 mg loading)	iv	3.0 mg/dl (3th day)	15.29	24th
					2.6 mg/dl (12th day)	7.69	
					4.1 mg/dl (21th day)	8.68	
					8.0 mg/dl (28th day)	11.39	
			Drug stopped				

(Continues)

TABLE 1 (Continued)

Non-COVID-19 patients						
Patient #	**Characteristics of patients**	**Weight (kg)**	**Voriconazole dosage**	**Route**	**Level and day of voriconazole[a]**	**CRP (mg/dl)**
14	50 years, female (non-critically ill)	75	200 mg q12h (2 × 450 mg iv loading)	po	0.97 mg/dl (7th day)	4.86
			200 mg q8h		4.7 mg/dl (18th day)	20.10
15	66 years, male (critically ill)	50	200 mg q12h (2 × 400 mg iv loading)	po	1.8 mg/dl (3th day)	22.40
16	47 years, male (critically ill)	65	200 mg q12h (2 × 400 mg iv loading)	po	4.2 mg/dl (4th day)	12.00
17	46 years, male (critically ill)	80	320 mg q12h (2 × 480 mg loading)	iv	5.0 mg/dl (6th day)	8.40
18	56 years, female (critically ill)	50	200 mg q12h (2 × 400 mg iv loading)	po	2.4 mg/dl (15th day)	8.40
					1.8 mg/dl (32th day)	20.70
					1.6 mg/dl (50th day)	4.26
19	55 years, female (critically ill	60	240 mg q12h (2 × 360 mg loading)	iv	0.2 mg/dl (6th day)	2.61
					0.8 mg/dl (8th day)	10.30
			360 mg q12h		4.7 mg/dl (12th day)	9.94
20	75 years, male (critically ill)	50	200 mg q12h (2 × 400 mg iv loading)	po	1.0 mg/dl (13th day)	3.24
					2.8 mg/dl (20th day)	9.84
					0.68 mg/dl (27th day)	1.37
21	67 years, male (critically ill)	75	300 mg q12h (2 × 450 mg loading)	iv	5.4 mg/dl (2th day)	7.78
					7.0 mg/dl (5th day)	0.73
			240 mg q12h		4.2 mg/dl (18th day)	4.24
22	29 years, female (critically ill)	55	220 mg q12h (2 × 330 mg loading)	iv	2.4 mg/dl (3th day)	12.30
23	68 years, female (critically ill)	70	280 mg q12h (2 × 420 mg loading)	iv	0.6 mg/dl (13th day)	7.28
			400 mg q12h		5.1 mg/dl (20th day)	9.11
24	46 years, male (critically ill)	70	280 mg q12h (2 × 420 mg loading)	iv	2.0 mg/dl (20th day)	1.82
					1.1 mg/dl (27th day)	1.86
					5.6 mg/dl (34th day)	17.20
					0.4 mg/dl (41th day)	7.81
					7.5 mg/dl (54th day)	16.90
			Drug stopped			
25	73 years, female (critically ill)	90	360 mg q12h (2 × 540 mg loading)	iv	6.8 mg/dl (5th day)	8.86
			300 mg q12h	po	7.0 mg/dl (10th day)	11.40
			200 mg q12h		4.9 mg/dl (16th day)	5.61
26	71 years, male (non-critically ill)	87	350 mg q12h (2 × 525 mg loading)	iv	4.0 mg/dl (4th day)	4.75
				po	7.1 mg/dl (14th day)	2.39
					7.1 mg/dl (23th day)	1.74
			300 mg q12h		3.8 mg/dl (34th day)	2.56
					3.4 mg/dl (42th day)	1.05

Abbreviations: CRP: C reactive protein; iv: intravenous.

[a]Trough levels of voriconazole was performed by liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays with the EUREKA® kit.

We suggest that in severe COVID-19 patients with a high-level inflammation, the risk of voriconazole toxicity may be higher. The fact that the trough level of voriconazole does not decrease despite the reduction of voriconazole dose could be explained by the decrease in hepatic clearance due to genetic polymorphism or inflammation. Since the presence of genetic polymorphism is not very common,

inflammation may be the possible triggered factor in these patients. Therefore, voriconazole levels may be monitored more frequently in COVID-19 patients, especially during the inflammatory phase. Additional pharmacokinetic studies are warranted in COVID-19 patient population to determine the appropriate dosing of voriconazole to assure therapeutic trough levels.

ACKNOWLEDGMENTS

P.B.E. was a major contributor in the study design, data analysis, result interpretation. E.K. and A.C.İ. contributed to design, analysis, interpretation of data, and revising the manuscript. A.G.E. contributed to writing and revising the manuscript. K.D. and O.U. critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Pinar Bakir Ekinci[1]
Emre Kara[1]
Ahmet Gorkem Er[2]
Ahmet Cagkan Inkaya[2]
Kutay Demirkan[1]
Omrum Uzun[2]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey*
[2]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*

Correspondence
Pinar Bakir Ekinci, Hacettepe University Faculty of Pharmacy, Department of Clinical Pharmacy, Sihhiye, Ankara, Turkey.
Email: pinar.bakir55@gmail.com

ORCID

Pinar Bakir Ekinci https://orcid.org/0000-0003-0694-6078

REFERENCES

1. Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis*. 2020;21(6):e149-e162. https://doi.org/10.1016/S1473-3099(20)30847-1
2. Elewa H, El-Mekaty E, El-Bardissy A, Ensom MH, Wilby KJ. Therapeutic drug monitoring of voriconazole in the management of invasive fungal infections: a critical review. *Clin Pharmacokinet*. 2015;54(12):1223-1235.
3. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. *Intensive Care Med*. 2020;46(6):1127-1153.
4. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis*. 2012;55(8):1080-1087.
5. Van Wanrooy MJ, Span LF, Rodgers MG, et al. Inflammation is associated with voriconazole trough concentrations. *Antimicrob Agents Chemother*. 2014;58(12):7098-7101.
6. Rieger JK, Reutter S, Hofmann U, Schwab M, Zanger UM. Inflammation-associated microRNA-130b down-regulates cytochrome P450 activities and directly targets CYP2C9. *Drug Metab Dispos*. 2015;43(6):884-888.