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COMMENTARY

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Suboptimal plasma concentrations with posaconazole suspension as prophylaxis in critically ill COVID-19 patients at risk of Covid-associated pulmonary aspergillosis

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Abstract

What is known and objective: The safety and efficacy of different antifungal agents in the prophylaxis of invasive fungal infection in patients with haematological disorders are known. We comment on the poor bioavailability of posaconazole suspension to suggest that it is not useful in critically ill COVID patients.

Comment: The increased mortality and high incidence of COVID-associated pulmonary aspergillosis (CAPA) might justify administration of off-label posaconazole for preventing CAPA, being the only drug officially registered for prophylaxis of fungal infections. We decided to initiate off-label posaconazole prophylaxis in COVID-19 patients, who were mechanically ventilated and exposed to high-dose steroids for progressive pulmonary disease or ARDS. We found that posaconazole suspension was inadequate. Very low trough levels were observed after administration, and the dose adjustments necessary for the therapeutic drug monitoring (TDM) of the drug in our critically ill ICU patients were not useful.

What is new and conclusion: Posaconazole suspension should not be used to prevent CAPA in COVID-19 patients on high-dose steroid therapy.

1 | WHAT IS KNOWN AND OBJECTIVE

In this journal, Leonart et al.[1] performed a systematic review and network meta-analysis to evaluate the safety and efficacy of different antifungal agents used for the prophylaxis of invasive fungal infection in patients with haematological disorders. Their elegant design was an inspiration for evaluation of prophylaxis of invasive fungal infection in intensive care unit (ICU) patients. We comment on the poor bioavailability of posaconazole suspension to suggest that it is not useful in critically ill COVID patients.

2 | COMMENT

Posaconazole is a triazole antifungal agent with potent activity against many clinically important yeasts and moulds.[2] Although posaconazole has some PK challenges, its efficacy as prophylaxis has been proved in randomized controlled trials (RCT) in neutropenic patients and severe graft-versus-host disease.[3,4]

Recently, it has been reported that secondary mould infections, also referred to as Covid-associated pulmonary aspergillosis (CAPA), frequently (20%–30%) occur in critically ill mechanically ventilated COVID-19 patients.[5] This association has also been reported with severe influenza infections in intensive care unit (ICU) patients.[6] In a recent prospective cohort of 108 critically ill patients with acute respiratory distress syndrome (ARDS), a higher 30-day mortality was observed in patients with CAPA (44% vs 19%).[7] Since March 2020, when COVID-19 manifested in Dutch hospitals, we found an incidence of possible CAPA in 25% of mechanically ventilated patients with COVID-19 and related ARDS in our ICU (unpublished data). Nearly all patients diagnosed with possible CAPA were exposed to steroid therapy (dexamethasone 8 mg/day and/or methylprednisolone 1 mg/

TABLE 1 Characteristics of critically ill COVID-19 patients who received posaconazole suspension as antifungal prophylaxis

Gender	Age (years)	Weight (kg)	Total posaconazole administrations during treatment	Sample after amount of gifts of posaconazole	Plasma concentration posaconazole (mg/L)	Interactions with other drugs
M	70	96.5	21	11	0.100	No
M	75	76.5	8	4 and 7	0.100 and 0.100	Pantoprazole
M	41	127	25	10	<0.100	o
M	69	79	13	6	<0.100	No
M	63	83	12	6 and 11	<0.100 and 0.400	No
F	67	110	15	13	0.200	Pantoprazole
M	57	70	16	15	0.300	No

kg/day). It is well known that steroid exposure may increase the risk of fungal infections in critically ill patients.[8] We decided to initiate off-label posaconazole prophylaxis in COVID-19 patients, who were mechanically ventilated and exposed to high-dose steroids (methylprednisolone 1mg/kg/day) for progressive pulmonary disease or ARDS. Patients received 200 mg tds suspension via a naso-gastric tube. As large inter-individual and intra-individual variation in bioavailability has been reported when administering posaconazole suspension in other critically ill patients (haematologic patients),[9] therapeutic drug monitoring (TDM) was performed. Posaconazole concentrations reach steady state 5–7 days after starting administration. In the literature, it has been reported that posaconazole plasma concentrations measured on day 2 are predictive for the steady-state level from day 7 onwards. The aim was to obtain trough levels on day 2 of >0.35 mg/L, which should predict trough levels of >0.7mg/L on day 7.[9] Patient characteristics are listed in Table 1. Seven patients in total received prophylactic posaconazole suspension. For all patients, except for two, we collected one sample. Two out of seven patients concomitantly used a proton pump inhibitor, which could have reduced the bioavailability of posaconazole.[2] We observed very low plasma concentrations (defined as concentrations below the above-mentioned TDM-targets) in 7 out of 7 patients and 9 out of 9 samples.

We should acknowledge that we made several assumptions when starting the posaconazole prophylaxis in ICU patients. Posaconazole is currently available in three formulations, one of which is posaconazole suspension. As posaconazole elimination half-life of the suspension is longer (7–10 days) than that of the other formulations (IV, Tablets; 6 days), it is uncertain if day 2 predicts for day 7. No samples in our patients have been taken on day 7, so we cannot state for certain that levels at steady state are subtherapeutic. This expectation is based on assumptions made for TDM of posaconazole in haematological patients. Posaconazole is reported to have significant pharmacokinetic (PK) variability. Contributing to this variability are dose, saturable absorption and intake of large amounts of food[2] In general, PK in critically ill patients can be highly variable due to several physiological factors such as hypoalbuminemia, influence of food, changed gastro-intestinal absorption, renal or hepatic dysfunction.[2] In addition, we were not able to adjust dosage or frequency, as advised by Dekkers et al.[9] This was caused by the acute ICU setting, where time is lacking to achieve steady state after a dose-adjustment of posaconazole.

Despite these limitations, we conclude that posaconazole suspension is highly inadequate for the above-mentioned patient population due to poor bioavailability, as proved by very low trough levels, and the difficulty to make adequate dose adjustments based on TDM in critically ill ICU patients.

3 | WHAT IS NEW AND CONCLUSION

Posaconazole suspension should not be used to prevent CAPA in COVID-19 patients on high-dose steroid therapy.

CONFLICT OF INTEREST

The authors do not declare any conflict of interest.

DATA AVAILABILITY STATEMENT

No additional data are available. Only the data presented in the table.

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