LETTER TO THE EDITOR

Therapeutic Drug Monitoring of Isavuconazole—But What about the Critically Ill?

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Abstract

Data on therapeutic drug monitoring of novel, broad-spectrum, and promising antifungal agent Isavuconazole sheds light on factors associated with subtherapeutic drug levels, however, a few other parameters, which characterize the critically ill patients, if included in the analysis, would have improved the understanding of drugs pharmacokinetics in this subset.

Keywords: Antifungal treatment, Isavuconazole, Pharmacokinetics in critically ill, Therapeutic drug monitoring.

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Dear Editor,

We thank the authors for publishing their extensive data on therapeutic drug monitoring (TDM) and pharmacokinetics of Isavuconazole in the Indian population.[1] We agree with their conclusion that TDM can help reduce treatment failures and adverse effects. Through this letter, we intend to argue that the study's design and findings have limitations that make it difficult to apply the results to the specific needs of intensivists and their patients.

Even though in almost 50% (29 of 50) of the study subjects the drug was started in ICU, the severity of illness scores like sequential organ failure assessment (SOFA) scores were not reported. No association was drawn between the severity of illness and drug levels by authors notwithstanding the fact that critical illness (including septic shock) alters the pharmacokinetics of drugs.[2]

The oral route of administration was used in all the patients included in the analysis. Though Isavuconazole's oral bioavailability is excellent (98%), to the best of our knowledge, data on oral absorption in critically ill and or patients in shock states is scarce.[3] Hypoperfusion, venous congestion, mucosal edema, and decreased splanchnic blood flow can affect a drug's absorption.[2] Besides many clinical trials involving the use of Isavuconazole in sicker patients used the intravenous route, at least for initial loading doses.[4] How oral administration affected the drug levels in the critically ill, is thus not clear from the paper.

Isavuconazole is available in intravenous and capsule formulations. Isavuconazole prescribing information states capsules should not be chewed, crushed, dissolved, or opened because the drug was not studied in this manner.[3] It recommends giving intravenous formulation instead of oral-capsule formulation by nasogastric tube (NGT) to patients unable to take medications by mouth. As all subjects in the study were suspected to be suffering from invasive fungal disease and many required treatments in the intensive care unit, it is evident that at least a fraction of them will be dependent on nasogastric feeding. Whether intravenous formulation or oral-capsule formulation was administered through nasogastric tubes to these patients is not explicit in the manuscript.

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Last but not the least, critically ill patients frequently need renal replacement therapy (RRT). Renal replacement therapy was not included by researchers in univariate or multivariate analysis for association with the distribution of Isavuconazole levels. Although dose modification of Isavuconazole has not been recommended for patients on RRT, some recent studies suggest that RRT is associated with subtherapeutic levels.[5] To conclude, we hail the efforts of the authors for enlightening us on the pharmacokinetics of Isavuconazole, however the inclusion of severity scores, effect of drug administration through NGT and the effect of RRT in an analysis of association with subtherapeutic drug levels, would have added significantly to the understanding of physicians caring for critically ill.

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References

1. Prayag PS, Soman RN, Panchakshari SP, Ajapuje PS, Mahale NP, Dhupad S, et al. Therapeutic drug monitoring of isavuconazole: Lessons learnt from a real-life setting in a Tertiary Care Center in India. Indian J Crit Care Med 2023;27(4):260–264. DOI: 10.5005/jp-journals-10071-24443.
2. Charlton M, Thompson JP. Pharmacokinetics in sepsis. BJA Educ. 2019;19(1):7–13. DOI: 10.1016/j.bjae.2018.09.006.

3. Astellas. Cresemba (isavuconazonium sulfate): Highlights of Prescribing Information. 2015. Available from: https://www.astellas.us/docs/cresemba.pdf.
4. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387(10020):760–769. DOI: 10.1016/S0140-6736(15)01159-9.
5. Perez L, Corne P, Pasquier G, Konecki C, Sadek M, Le Bihan C, et al. Population Pharmacokinetics of Isavuconazole in Critical Care Patients with COVID-19-Associated Pulmonary Aspergillosis and Monte Carlo Simulations of High Off-Label Doses. J Fungi (Basel) 2023;9(2):211. DOI: 10.3390/jof9020211.