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Letter to the Editor

Protease inhibitors and azolic antifungals in HIV patients with histoplasmosis: a clinical pharmacokinetics perspective



Dear Editor,

A previous *in vitro* investigation found that a synergistic effect might occur, when using itraconazole (ITRA) and ritonavir (RTV) against *Histoplasma capsulatum*,¹ where an interesting mechanism of action was proposed. However, relevant pharmacokinetic (PK) issues were under explored. Herein, this letter attempts to deepen a clinical PK discussion not performed by Brillhante and colleagues.¹

Firstly, the *in vitro* model¹ did not account for drug penetration in macrophages, given that *Histoplasma* spp. are found as intracellular microorganisms after innate immunity recognition and phagocytation.² Secondly, one should recognize the potential CYP3A4 competitive inhibition when using RTV and an azolic agent. By combining them, we expect an elevated plasma concentration of the azolic agent,³ as RTV has higher affinity to the aforementioned phase 1 enzyme, but not the opposite.¹ The association of both drugs is a possible scenario⁴ when treating multiple drug resistant HIV infected patients. Whether non-CYP3A4 substrates are unavailable, clinicians should attempt to monitoring hepatic enzymes and random ITRA steady state serum concentrations (>1 µg/mL) after 7–15 days.³

Finally, the previous report¹ discussed that using both drugs might be clinically possible by “reducing itraconazole dose”. For several reasons,⁵ there is no evidence on lowering ITRA doses: (a) it has an erratic gastrointestinal absorption and food composition and gastric pH might influence drug’s bioavailability (cyclodextrin-containing formulations are preferred); (b) ITRA has non-linear PK, thus, dose reductions may lead to unpredictable serum levels (zero order kinetics is dependent on enzyme saturation).

REFERENCES

1. Brillhante RS, Caetano ÉP, Riello GB, et al. Antiretroviral drugs saquinavir and ritonavir reduce inhibitory concentration values of itraconazole against *Histoplasma capsulatum* strains *in vitro*. *Braz J Infect Dis*. 2016;20:155–9.
2. Porta A, Maresca B. Host response and *Histoplasma capsulatum*/macrophage molecular interactions. *Med Mycol*. 2000;38:399–406.
3. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–25.
4. Nacher M, Adenis A, Aznar C, et al. How many have died from undiagnosed human immunodeficiency virus-associated histoplasmosis, a treatable disease? Time to act. *Am J Trop Med Hyg*. 2014;90:193–4.
5. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. *J Antimicrob Chemother*. 2005;56 Suppl 1:i17–22.

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Conflicts of interest

The author declares no conflicts of interest.