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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 sinergistic 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 Brilhante and colleagues.[1]

Firstly, the *in vitro* model[1] 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 scenario[4] 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 report[1] 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).

Conflicts of interest

The author declares no conflicts of interest.

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