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, 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 model1 did not account for drug penetration in macrophages, given that Histoplasma spp. are found as intracellular microorganisms after innate immunity recognition and phagocytosis.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. 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).

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES


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