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Are fluconazole or sertraline dose adjustments necessary with concomitant rifampin?

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Dear Editor

Among HIV-infected persons with tuberculosis (TB) and fungal opportunistic infections, fluconazole and rifampin are frequently co-administered. High dose fluconazole (800mg/day) is typically used for consolidation therapy in cryptococcal meningitis as well as for primary induction therapy in many low income countries where amphotericin is unavailable. Preemptive fluconazole is recommended for HIV-infected persons with early disseminated, asymptomatic cryptococcal antigenemia (1). Additionally, sertraline is an emerging, possible antifungal medicine with demonstrated activity *in vitro*, *in vivo*, and in a phase II human trial (2, 3).

Rifampin is a strong inducer of the hepatic cytochrome P450 (CYP) 2C9, 2C19, and 3A4 pathways that are used in fluconazole and sertraline metabolism. Prior Thai pharmacokinetic studies demonstrate increased fluconazole clearance with concomitant rifampin (4). Thus, some clinicians anecdotally increase fluconazole dosing by 50% in the presence of rifampin, though guidelines provide no firm recommendations for dose adjustments. We evaluated fluconazole and sertraline plasma levels in the presence or absence of rifampin in Ugandans with cryptococcal meningitis during 2013–2014 (2). We evaluated mean steady state CSF and plasma fluconazole levels in 68 participants who received fluconazole 800mg daily and 9 participants who additionally were already receiving rifampin 600mg daily at study entry. We also evaluated mean steady state plasma sertraline in 31 participants who received sertraline 400mg daily, and in 9 participants who additionally were receiving rifampin 600mg daily. All participants had fluconazole or sertraline levels measured at 7, 10, 14, and/or 28 days after initiating their respective antifungal medication. Steady state was defined as the average of these measurements.

As seen in Figure 1, mean steady state fluconazole levels did not differ in the presence or absence of rifampin ($P=.58$). However, mean steady state sertraline levels averaged 50% lower in the presence of rifampin ($P<.001$)

In sub-Saharan African where mortality from cryptococcal meningitis remains high at 70% due to medication shortages, and limited resources, appropriate dosing of antifungals remains critical (5). Fluconazole steady state levels remained unchanged in the presence of rifampin in this African population while sertraline plasma steady state levels were 50% lower in the presence of rifampin. Further evaluation of drug levels and clinical outcomes in cryptococcal meningitis patients receiving these drug combinations would further elucidate any clinical significance of these drug interactions.

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Figure 1. Fluconazole and Sertraline Plasma levels with or without rifampin

Mean fluconazole levels with rifampin 41.1 µg/mL (95% CI, 32 to 51) did not differ from fluconazole levels without rifampin of 43.8 µg/mL (95% CI, 39 to 49; $P=.58$). Mean sertraline levels with rifampin 208 µg/mL (95% CI, 130 to 285) were 50% lower than sertraline levels without rifampin of 416 µg/mL (95% CI, 350 to 484; $P<.001$).