The pharmacodynamics of Sertraline as Anti-fungal

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Objective: To determine a sertraline dose associated with the fastest rate of fungal clearance from cerebrospinal fluid (CSF) and to quantify the clinical benefits of sertraline when added to amphotericin B and fluconazole for the treatment of HIV-associated cryptococcal meningitis.

Methods: A Poisson regression was used to model log-transformed fungal counts in CSF obtained from ASTRO-CM pilot study and COAT trial for the calculation of CSF fungal clearance rate (log₁₀ CFU/mL/day). Correlations of counts within a patient was accounted for using a three-state Markov model to represents an increase, decrease or no change in log₁₀ CFU/mL from a previous day. A mono-exponential decline with a random effect was also added as a time-effect. Estimated fungal clearance rates were compared among sertraline doses ranging from 100–400 mg daily for the selection of optimal dose. To determine the clinical benefit sertraline, overall fungal clearance from ASTRO-CM was compared to that of COAT trial which served as a control. A previously developed PK model of sertraline in HIV patients was used with the measured minimum inhibitory concentrations (MICs) of sertraline against Cryptococcus isolates to simulate, calculate and explore the relationships of various PK/PD indices with the daily change in log₁₀ CFU/mL. Time-to-death analysis was performed to calculate the survival probability over time as a clinical outcome

Results: Rate of CSF fungal clearance was similar among 100, 200, 300, and 400 mg of sertraline. The addition of sertraline increased fungal clearance by 38% relative to standard therapy alone. Cumulative AUC/MIC of 50 mcg/mL was associated with 2.5 log reduction in log₁₀ CFU/mL/day. Female and 400 mg of sertraline daily had lower 2-week survival rate.

Conclusion: Sertraline increased the rate of CSF fungal clearance independent of dose and whether a patient was on anti-retroviral therapy or not. Yet, no survival benefit was observed likely to due to lack of power. A well-powered, randomized clinical trial is required to evaluate the potential survival benefit of sertraline.