Optimization of the Dosage of Flucytosine in Combination with Amphotericin B for Disseminated Candidiasis: a Pharmacodynamic Rationale for Reduced Dosing

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Flucytosine (5FC) and amphotericin B have an additive effect when used for disseminated candidiasis. Here, we bridge the results of an experimental pharmacodynamic study to humans and demonstrate that a 5FC dosage of 25 mg/kg of body weight/day in four divided doses in combination with amphotericin B produces near-maximal effect.

Bridging from experimental systems to humans is increasingly used as a tool to further explore the clinical implications of experimental data (3, 8, 9). The combination of amphotericin B and flucytosine (5FC) is used to treat disseminated candidiasis. The standard dosage of 5FC of 150 mg/kg of body weight/day in combination with amphotericin B at 0.5 to 1.0 mg/kg/day frequently results in peak 5FC levels greater than 100 mg/liter, which are associated with toxicity (6). Recently, we demonstrated that the combination of amphotericin B and 5FC is additive in a murine model of disseminated candidiasis (10). Here, we bridge these experimental results to humans to generate hypotheses regarding the optimal clinical dosages of these antifungal agents when administered concomitantly.

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The steps undertaken in the in vivo-to-human bridging process are summarized in Table 1. The Greco equation was used for the interaction effect modeling (7, 10). This model takes the form

\[
1 = \frac{D_{\text{AmB}}}{EC_{50, \text{AmB}} \cdot [E/E_{\text{con}} - E]} + \frac{D_{\text{5FC}}}{EC_{50, \text{5FC}} \cdot [E/E_{\text{con}} - E]} + \frac{\alpha \cdot D_{\text{AmB}} \cdot D_{\text{5FC}}}{EC_{50, \text{AmB}} \cdot EC_{50, \text{5FC}} \cdot [E/E_{\text{con}} - E]} \left(\frac{E_{\text{con}}}{E_{\text{con}} - E}\right)
\]

where \(E_{\text{con}}\) is the fungal burden in the absence of therapy; \(D_{\text{AmB}}\) and \(D_{\text{5FC}}\) are the drug exposures of amphotericin B and 5FC, respectively, producing the effect \(E\); \(EC_{50, \text{AmB}}\) and \(EC_{50, \text{5FC}}\) are the drug concentrations producing 50% of the maximum effects of amphotericin B and 5FC, respectively; \(n_{\text{AmB}}\) and \(n_{\text{5FC}}\) are the respective Hill (slope) constants; and \(\alpha\) is the interaction parameter. The amphotericin B MIC of the experimental strain was 0.03 mg/liter (determined using a microdilution modification of CLSI [formerly NCCLS] methodology [12] with the addition of antibiotic medium 3; the MIC\(_{90}\) for 4,247 Candida albicans strains in our laboratory using this method is 0.125 mg/liter). The 5FC MIC using CLSI methodology (12) was 0.125 mg/liter, and the published MIC\(_{90}\) using this methodology is 1 mg/liter (13).

To bridge the results from experimental models to humans, drug exposure must be transformed from a measure quantified with respect to the host (i.e., dose) to one made with respect to the common microbiological target; the latter is achieved by using the pharmacokinetic/pharmacodynamic ratio that best links drug exposure to the observed effect (Table 1). In this process, the MIC serves as a measure of antifungal drug potency for the microbiological target for both the experimental system and simulated humans. In the case of amphotericin B, we used the area under the concentration-time curve (AUC)/MIC ratio as the dynamically linked variable. While we could have used the maximum concentration of drug in serum (C\(_{\text{max}}\)/MIC ratio (1, 14), in our experimental model, amphotericin B was administered only once, thus ensuring complete colinearity between the C\(_{\text{max}}\)/MIC and AUC/MIC ratios (10). The administration of more than one dose (as occurred in the simulations [described below]) may potentially lead to a degree of dissociation between the C\(_{\text{max}}\)/MIC and AUC/MIC ratios; consequently, we may have induced a degree of bias if the former is truly linked with outcome. For 5FC, the percentage of time above the MIC (%T\(_{\text{MIC}}\)) was employed as the dynamically linked variable, as previously described (2). Nath et al. (11) described the population pharmacokinetics study...
of amphotericin B in children. The pharmacokinetic parameters from this model were scaled and applied to a 70-kg human. In the case of 5FC, the model of Ette et al. was used (5).

For the Monte Carlo simulations, the mean pharmacokinetic parameter values were embedded within ADAPT II (4). The simulations suggested that 25 mg/kg/day administered in four divided dosages resulted in a %T\textsubscript{MIC} of 100% for all patients—this was the case for isolates with MICs of ≤1 mg/liter. Notably, this dosage is significantly less than the currently recommended 100 to 150 mg/kg/day. Subsequently, the AUC from 0 to 24 h (AUC\textsubscript{0-24})/MIC ratio at steady state for 800 simulated patients receiving amphotericin B at 0.1, 0.3, and 0.6 mg/kg/day was also determined.

The mean parameter estimates from the drug interaction model were inserted into ADAPT II. The AUC\textsubscript{0-24}/MIC and %T\textsubscript{MIC} values (for amphotericin B and 5FC, respectively) at steady state that developed following the administration of the drugs alone and in combination to each of the 800 simulated patients were calculated and then inserted into the Greco equation. The residual fungal burden in each individual was calculated, and the overall effect for the simulated population was determined.

Amphotericin B at 0.1, 0.3, and 0.6 mg/kg/day administered as monotherapy resulted in mean (± standard deviation) residual fungal burdens of 2.2 ± 0.28, 1.0 ± 0.18, and 0.6 ± 0.11 log\textsubscript{10} CFU/g, respectively (Fig. 1A, C, and E). The concomitant administration of 5FC at 25 mg/kg in four divided dosages with amphotericin B resulted in a small additional fungicidal kill relative to that observed with amphotericin B alone (Fig. 1B, D, and F). This additional fungicidal effect was largest for the combination of amphotericin B at 0.1 mg/kg with 5FC at 25 mg/kg (i.e., the decline was 0.7 log\textsubscript{10} CFU/g); for amphotericin B at 0.3 and 0.6 mg/kg, the additional effect was smaller (0.15 and 0.1 log\textsubscript{10} CFU/g, respectively); this was because these higher dosages of amphotericin B had induced a near-maximal reduction in fungal burden.

Thus, two conclusions are possible from these simulations: (i) the addition of 5FC to amphotericin B administered in a standard clinical dosage for disseminated candidiasis (i.e., 0.6 mg/kg) results in relatively little additional fungicidal effect since this human dosage results in drug exposures which induce near-maximal reduction in fungal burden; (ii) if 5FC is to be used, dosages in excess of 25 mg/kg/day are not associated with additional fungicidal effect for the vast majority of Candida isolates and may unnecessarily expose patients to the risk of drug-related toxicity.

Therefore, the principal advantage of the bridging process is the ability to generate a number of refined and clinically pertinent hypotheses which are suitable for further study at the bedside. Importantly, the conclusions of this paper do not necessarily apply to isolates of C. albicans which exhibit high-level amphotericin B and/or 5FC resistance, infections within sanctuary sites, and non-Candida yeasts such as Cryptococcus neoformans. The findings of this study should prompt a reevaluation of the dosage of 5FC used in combination with amphotericin B for the treatment of disseminated candidiasis.
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REFERENCES


