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Title: Pharmacodynamics of Isavuconazole in a Rabbit Model of Cryptococcal Meningoencephalitis

Running Title: Pharmacodynamics of Isavuconazole in Cryptococcosis

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ABSTRACT

Cryptococcus spp., an important fungal pathogen, is the leading cause of fungal-related mortality in human immunodeficiency virus patients, and new therapeutic options are desperately needed. Isavuconazonium sulfate, a newer triazole antifungal agent, was studied to characterize the exposure–response relationship in a rabbit model of cryptococcal meningoencephalitis. Isavuconazonium sulfate treatment was compared with fluconazole and untreated controls. Fungal burden in the cerebrospinal fluid was measured serially over time, while yeast concentrations in the brain and the eye (aqueous humor) were determined at the end of therapy. The exposure impact of isavuconazonium sulfate dosing in the rabbit was linked using mathematical modeling. Similar significant reductions in fungal burden in the brain and cerebrospinal fluid were observed with isavuconazonium sulfate and fluconazole treatment compared with untreated controls. No dose-dependent response was demonstrated with isavuconazonium sulfate treatment in this study. The treatment of cryptococcal meningoencephalitis with isavuconazonium sulfate was similar to that with fluconazole. Dose-dependent reductions in yeast over time were not demonstrated, which limited our ability to estimate the pharmacodynamic target. Further non-clinical and clinical studies are needed in order characterize the extent of the exposure–response relationship in cryptococcal meningoencephalitis. However, this study suggests isavuconazonium sulfate, like fluconazole, could be beneficial in the setting of consolidation and maintenance

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46 therapy, rather than induction monotherapy with high burden cryptococcal

47 meningoencephalitis.

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INTRODUCTION

Infections caused by *Cryptococcus neoformans* and *C. gattii* are associated with excessive morbidity and mortality in patients with and without HIV. *C. neoformans* is the leading cause of fungal-related mortality in HIV patients, especially in sub-Saharan Africa where the HIV/AIDS epidemic is persistent (1). At the peak of the HIV epidemic, approximately 1 million cases of cryptococcosis were reported annually in patients with AIDS (1). In the developed world, cases of cryptococcosis declined over the same time period as the use of antiretroviral therapy increased. In contrast, the prevalence remained high in low to middle income countries (2). In the United States, it is estimated that nearly 3,400 hospitalizations occur yearly due to cryptococcal meningitis (3). Direct hospitalization-associated costs for cryptococcal meningitis amounted to approximately US$54 million in 2009 (3).

Treatment of cryptococcal meningitis typically includes induction therapy with amphotericin B deoxycholate (0.7–1.0 mg/kg per day) or AmBisome (3–4 mg/kg per day intravenously) plus flucytosine (100 mg/kg per day orally) in four divided dosages for 1 week, followed by consolidation therapy with fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks (4). In some areas of the world, fluconazole may be the only available agent for induction therapy (4). High baseline cerebrospinal fluid (CSF) fungal burden, altered mental status, older age, and high peripheral white blood counts predict acute 2-week mortality. Furthermore, improved outcomes were associated with amphotericin-based treatment and prompt immune reconstitution with antiretroviral therapy (5).

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Cryptococcal infection generally begins in the lungs, although meningitis is the most frequently encountered clinical manifestation of cryptococcosis among those with advanced immunosuppression. The disease is more properly characterized as “meningoencephalitis” rather than meningitis since the brain parenchyma is almost invariably involved on histologic examination (6). This understanding is critical when determining a successful treatment strategy, as central nervous system (CNS) penetration into the brain tissue as well as into the CSF is vital to improve outcome.

Isavuconazonium sulfate, the water-soluble prodrug of the broad-spectrum triazole antifungal agent isavuconazole, is approved by the U.S. FDA for the treatment of invasive aspergillosis and invasive mucormycosis, and by the European Medicines Agency for the treatment of invasive aspergillosis, and invasive mucormycosis in patients for whom amphotericin B is inappropriate (7, 8) (9). Isavuconazole MIC values against *Cryptococcus spp*. range from 0.008 mg/L to 0.5 mg/L with an overall modal MIC of 0.03 mg/L in a collection of more than 800 *Cryptococcus neoformans* isolates (10).

To further support an understanding of the effectiveness of isavuconazonium sulfate against cryptococcal infections, particularly in the CNS, we characterized the exposure–response relationship of isavuconazonium sulfate in a well-established rabbit model of cryptococcal meningoencephalitis caused by *Cryptococcus neoformans*.

RESULTS

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Cryptococcus neoformans (H99) MIC values. The geometric mean isavuconazole MIC value for the H99 strain of *Cryptococcus neoformans* was 0.008 mg/L for isavuconazole and 1 mg/L for fluconazole. Yeast grown from treatment Day 8 of the isavuconazonium sulfate treatment animals showed similar MIC values.

Animal model. Significant reductions in fungal burden were seen in the brain following administration of isavuconazonium sulfate doses of 83 mg/kg (equivalent to 45 mg/kg of isavuconazole) and 111.8 mg/kg (equivalent to 60 mg/kg of isavuconazole). These were comparable to 80 mg/kg of fluconazole. Both isavuconazonium sulfate and fluconazole treatments resulted in significant decreases in fungal burden in the brain compared with untreated controls (P = 0.0003; P = 0.0002; P = 0.0034, one-way analysis of variance (ANOVA), Holm–Šidák's multiple comparisons test) (**Fig. 1a**). Treatment with isavuconazonium sulfate and fluconazole resulted in significant reductions in the CSF fungal burden of yeast over time compared with controls (P < 0.0001, two-way ANOVA, Tukey's multiple comparisons test) (**Fig. 1b**). Investigation of the residual fungal burden in the eye (aqueous humor) were extremely variable and were not considered reliable; therefore, the results are not reported here.

Pharmacokinetics. Mean isavuconazole concentrations in the brain tissue (cerebrum, cerebellum, meninges) at the end of the experiment were similar between the isavuconazonium sulfate dose groups (**Table 1**). The mean ratio of brain to plasma isavuconazole concentrations in rabbits was 0.69 and 0.42 for the 83.8 mg/kg and 111.8 mg/kg doses, respectively. As with the brain tissue, the

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mean isavuconazole concentrations in the CSF did not increase with increasing dose (**Table 1**). The mean ratio of CSF to plasma ratio was 0.044 and 0.019 for the 83.8 mg/kg and 111.8 mg/kg doses, respectively (**Table 1**).

Pharmacokinetic/pharmacodynamic modeling.

Pharmacokinetic/pharmacodynamic modeling using the brain isavuconazole concentration data and fungal burden in the CNS was not possible because of the lack of temporal data for measures. Therefore, the pharmacokinetic/pharmacodynamic model focused on a link between plasma and CSF isavuconazole concentrations and CSF fungal burden over time.

The fit of the model to the plasma and CSF isavuconazole concentration data and yeast colony-forming units in the CSF over time was acceptable based on visual inspection of the median observed-versus-predicted plots. A linear regression had a coefficient of determination (r^2) of 0.841 (slope = 0.951), 0.745 (slope = 0.958), and 0.692 (slope = 0.853) after the Bayesian step for the isavuconazole concentrations in the plasma, CSF and CSF fungal burden, respectively (**Fig. 2a, b** and **c**). The estimates of bias and imprecision were also acceptable (plasma: −0.122 and 1.19; CSF: −0.0246 and 2.02: CSF CFU: 0.00863 and 0.0207). The observed-versus-predicted plots using the mean parameter values were similar (data not shown). The mean parameter estimates are included in **Table 2**.

The median Bayesian posterior pharmacokinetic parameters from the pharmacokinetic/pharmacodynamic model were used to estimate the area under the concentration-time curve from 0 h to 24 h ($AUC_{0–24}$) for the plasma and CSF,

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as well as the area under the CSF fungal burden-versus-time relationship (**Table 3**). Although there was a nearly twofold increase in the plasma isavuconazole exposures, drug exposure in the CSF did not increase. Not surprisingly, this lack of increase in exposure by dose in the CSF compartment resulted in minimal differences in response by dose (**Table 3**). This lack of change in exposure and effect by dose resulted in the inability to explore and characterize the pharmacodynamic target (50% effective concentration) for response in the inhibitory sigmoid Emax model with this dataset.

DISCUSSION

Treatment options for cryptococcal infections are limited and the available antifungal agents have not changed substantially in the last ~20 years. It was not until recently that characterization of the exposure–response relationship with animal models and bridging studies became available to guide dosing in clinical studies (11, 12). These efforts led to modifications in sequence and duration of induction therapy, as well as changes to dosage of the three recommended agents: amphotericin B, flucytosine, and fluconazole (4). Access to all three medications in countries with limited resources—where the incidence of the infection is highest—is inconsistent (2). Fluconazole is the only agent available in some of these countries. In the current study, isavuconazonium sulfate demonstrated significant reductions in CSF and brain fungal burden in rabbits infected with *Cryptococcus neoformans* (H99) compared with untreated rabbits,

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and similar to fluconazole. However, a dose-dependent response was not demonstrated for isavuconazole for the dosages used in this study.

Isavuconazonium sulfate regimens used to treat invasive mold infections result in total drug plasma AUCs of approximately 90 mg*h/L (13). There is limited data on CNS penetration. One report that details the response of patients receiving isavuconazonium sulfate dosages ranging from 372 mg (equivalent to 200 mg isavuconazole) to 1,116 mg/day (equivalent to 600 mg isavuconazole) is available (14). CSF concentrations measured during treatment are summarized in **Table 4**. The ratio of CSF to plasma was consistently 0.008:0.011 and did not increase with increasing dose. If one assumes similar CSF penetration from rabbits to humans, the CSF concentrations achieved with doses above 372 mg/day are closer to those concentrations observed in the rabbits. Limited data are available on human brain concentrations of isavuconazole reporting a brain to plasma ratio from one patient of 0.9 (15).

Given that a significant proportion of the clinical impact of cryptococcal disease in humans relates to involvement of the brain, the extent of penetration into the cerebral parenchyma is important. Data from radiolabeled isavuconazonium sulfate administered to rats show a brain to plasma concentration ratio of approximately 1.8:1 (16). A similar ratio has been reported from infected mice after receiving isavuconazonium sulfate for 14 days (17). An *in vivo* model of CNS disease has been conducted with isavuconazonium sulfate in mice infected with two strains of *Cryptococcus neoformans* (USC 1597 and H99) (17). Significant improvements in survival and reductions in fungal burden

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in the cerebrum were observed with isavuconazonium sulfate treatment compared with controls and the effects were similar to treatment with fluconazole.

In the clinical setting, nine patients diagnosed with cryptococcosis were treated with isavuconazonium sulfate in an open-label study (VITAL study) (18). Eight patients were alive through ≥84 days and six were considered to be treatment successes.

As some yeasts persisted in the subarachnoid space for 12 days after treatment, we checked several colonies from the rabbit CSF after 8 days of treatment and there was no change in their original MICs, suggesting no evidence of direct selection for drug-resistant isolates (data not shown). Yeasts showed a non-significant reduction in the eyes following treatment with both isavuconazonium sulfate and fluconazole compared with untreated controls.

The current study has several limitations. First, there was insufficient data available to understand the temporal drug exposure in the cerebrum and eyes, eliminating an ability to characterize the exposure–response relationships in these tissues. Only a single yeast strain was studied in the rabbit model, which limits an ability to understand the potential impact of pharmacodynamic variability on the clinical utility of isavuconazonium sulfate for cryptococcal meningitis. Despite these limitations, treatment with isavuconazonium sulfate and fluconazole provided similar significant reductions in cryptococcal burden in both brain and CSF. Additional preclinical and clinical studies are required to further

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define the clinical utility and potential indications of isavuconazonium sulfate for cryptococcal meningoencephalitis.

MATERIALS AND METHODS

Organism. A clinical strain of *Cryptococcus neoformans* (H99) was used. H99 yeasts were stored at −80°C in 25% glycerol. Isavuconazole and fluconazole MICs were tested using the CLSI M27-A3 macrodilution methodology. Briefly, RPMI 1640 broth, using an inoculum of 0.5×10^3 to 2.5×10^3 CFU/mL, was incubated for 72 h at 35°C. The endpoint for determination of the MIC was defined as ≤50% reduction in growth relative to the growth of control yeasts without drug exposure.

Rabbit model of cryptococcal meningitis. Male New Zealand white rabbits weighing 2–3 kg were used; this model has been previously described (12). The Duke University IACUC approved the protocol prior to study initiation.

Rabbits were individually housed and maintained with water and standard rabbit feed *ad libitum*. Immunosuppression was induced using hydrocortisone acetate 5 mg/kg by intramuscular injection daily starting on Day −1 and continuing through Day 13 post-infection. Rabbits were given hand-fed vegetables and supplemental subcutaneous fluids throughout the study. They were weighed daily throughout the study. Rabbits were sedated with an intramuscular injection of a mixture of ketamine (30 mg/kg) and xylazine (3 mg/kg) prior to intracisternal inoculation and cisternal taps. Intravenous (i.v.) yohimbine was used to reverse the sedation, and rabbits were recovered under

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supplemental heat with continuous monitoring. Prior to euthanasia, rabbits were sedated with ketamine and xylazine (40 mg/kg and 5 mg/kg, respectively).

Pharmacokinetic blood collections. Collection was performed on Day 8 post-infection. For pharmacokinetic blood draws, rabbits were sedated with acepromazine, 1 mg/kg, and a catheter was placed in the ear artery and sutured in place. For each blood draw, the catheter was flushed with heparinized saline. A pre-sample was then collected and discarded to remove any residual heparin and then the sample was collected from the catheter. Blood samples were taken in EDTA plasma separator tubes at the indicated timepoints post-drug administration. Plasma was isolated by centrifugation and stored at −80^{o}C prior to testing.

Pharmacokinetic Tissue collections and processing. Brain and meningeal tissue was collected at the end of the experiment. Tissue samples were weighed and transferred to a homogenization tube. The weight was multiplied by 3 for brain and 5 for meninges to adjust the volume of the reconstitution solvent to the samples. Tissues were homogenized for 30 seconds at 4 m/s and repeated as necessary.

Inoculation. *C. neoformans* isolate, strain H99, was grown at 30°C for 2–3 days on yeast extract-peptone-dextrose (YPD) plates. A single colony was selected and a 25 mL YPD broth culture was initiated and grown for 2 days at 30^{o}C in a shaker incubator. The organisms were washed twice in phosphate-buffered saline (PBS) and diluted to 3.9 × 10^{6} cells/mL in PBS. In previous studies, we used 1 × 10^{8} cells of *C. neoformans* per inoculation, but a pilot study

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indicated that a lower inoculum, 1×10^6 cells, was required for a 14-day study. A volume of 0.3 mL of inoculum was loaded into 3 mL syringes with 25-gauge needles. The yeast inoculum was administered by injecting 0.3 mL intracisternally on Day −2 before dosing. The rabbits were injected with yohimbine, 0.2 mg/kg i.v. As mentioned above, rabbits were given supplement subcutaneous fluids during recovery from sedation.

Treatment. Isavuconazole was administered as a water-soluble prodrug, isavuconazonium sulfate, via oral gavage. The drug was stored in sterilized glass vials at −20°C. Prior to dosing each day, an aliquot was removed and a volume of pH 4 USP-grade water was added to the aliquot to yield a solution of 60 mg/mL of prodrug. Prodrug doses included 83.8 mg/kg and 111.8 mg/kg once daily, which delivered 45 mg/kg and 60 mg/kg, respectively, of isavuconazole to the animal. Fluconazole was purchased as an oral suspension and administered i.v. at a dose of 80 mg/kg per day. It was reconstituted with USP water to a final concentration of 40 mg/mL. Untreated controls received saline. Drug dosing began 48 hours post-inoculation and continued for 12 consecutive days.

Fungal burden of tissue. All rabbits were humanly sacrificed after the final CSF collection, either on Day 10 or at the time of sacrifice. Brains were removed and then dissected sagittally for quantitative cultures and drug-level analysis. Fungal burden was measured in brain (cut into three sections) and eyes (vitreous humor and aqueous humor). Tissue was placed in pre-weighed tubes containing 1 mL of PBS and then weighed again to find the net weight of the tissue. Tissue was homogenized using a Pro200 (Pro Scientific, Oxford, CT, USA) in a

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biological safety cabinet. The tissue homogenates were 10-fold serially diluted, and then plated on YPD with chloramphenicol agar. Cultures were grown for 3 days at 30°C. CFUs were quantified as the CFU/g of tissue. The fungal burden within the CSF from the subarachnoid space was measured from serial samples taken at 48, 96, 144, 192, and 240 h post-inoculation via an intracisternal tap with a 3 mL syringe and a 25-gauge needle, serially diluted (1:10), in PBS in 1 mL and plated on YPD with chloramphenicol agar, and incubated at 30°C for 2–3 days, then viable yeast colonies were counted. Calculations for CFU/mL were as follows: (CFU counted × dilution)/0.1 mL. The remaining CSF was centrifuged, and the supernatant stored at −80°C.

Isavuconazole bioanalytical assay. Isavuconazole concentrations in rabbit plasma, CSF and brain were measured using a Thermo Fisher Scientific Vanquish (Waltham, MA, USA) ultraperformance liquid chromatography coupled with a Thermo Fisher Scientific Q Exactive™ Focus (Waltham, MA, USA) mass spectrometer. The method used an ACE 5 C18-AR 50 × 3.0 mm (supplier: Hichrom Ltd, Reading, UK) and a 3 µL injection volume. A standard curve encompassing 15 to 40,000 ng/mL was constructed from stock solutions of isavuconazole 1 mg/mL in dimethyl sulfoxide. Chromatographic separation was achieved using gradient conditions starting with 35:65 (0.1% formic acid in water as mobile phase A, and 0.1% formic acid in acetonitrile as mobile phase B). Mobile phase B was increased to 95% from 0.2 to 1.0 min and held for 1.6 min. At 1.7 min mobile phase B was reduced to 65%. This was all at a flow rate of 0.6 mL/min. Isavuconazole was detected using the exact mass in positive ion mode

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(438.1195). Isavuconazole eluted after 1.0 min. The limit of detection was 15 ng/mL and the assay was linear over the concentration range 15 to 40,000 ng/mL. The quality control intra- and inter-day accuracy was 98.7–104.6%. The quality control coefficient of variation percentage was 1.1–8.4%.

Pharmacokinetic/pharmacodynamic mathematical modeling. Population pharmacokinetic/pharmacodynamic mathematical modeling was performed using non-parametric estimation, Pmetrics™ (v. 1.5.2, University of Southern California, Los Angeles, CA, USA) (19) and fitted to the rabbit plasma and CSF isavuconazole concentration data, and the CSF CFUs. Data were weighted by the inverse of the estimated assay variance. The linked pharmacokinetic/pharmacodynamic model was constructed using the following set of differential equations:

Eq. 1 $$\frac{dX(1)}{dt} = -Ka \cdot X(1)$$

Eq. 2 $$\frac{dX(2)}{dt} = Ka \cdot X(1) - \left(\left(\frac{Cl}{V}\right) \cdot X(2)\right) - Kcp \cdot X(2) + Kpc \cdot X(4) - Kcm \cdot X(2) + Kmc \cdot X(3)$$

Eq. 3 $$\frac{dX(3)}{dt} = Kcm \cdot X(2) - Kmc \cdot X(3)$$

Eq. 4 $$\frac{dX(4)}{dt} = Kcp \cdot X(2) - Kpc \cdot X(4)$$

Eq. 5: $$\frac{dX(5)}{dt} = Kgmax \cdot \left(1 - \left(\frac{\left(\frac{X(3)}{V}\right)^{Hg}}{C50g^{Hg} + \left(\frac{X(3)}{V}\right)^{Hg}}\right)\right) \cdot X(5) \cdot \left(1 - \left(\frac{X(5)}{popmax}\right)\right) - kkmax \cdot X(5) \cdot \left(\frac{\left(\frac{X(3)}{V}\right)^{Hk}}{C50g^{Hk} + \left(\frac{X(3)}{V}\right)^{Hk}}\right)$$

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The first four equations describe the pharmacokinetics of the isavuconazole, (compartment 1, theoretical absorptive compartment for oral administration; 2, central compartment; 3, CSF compartment; and 4, peripheral compartment). Cl is the clearance and defined as the amount of drug being cleared from the central compartment over time, and V is the volume of the central compartment. Ka is the first order absorption constant; Kcp, Kpc, Kcm, and Kmc are the rate constants describing the flow of drug to and from compartments 2, 3, and 4. Equation 5 describes the rate of change of the *Cryptococcus* yeasts as $\log_{10}$ CFU/mL of CSF. Kgmax represents the maximum rate of growth; Hg is the slope function for growth; C50g is the amount of drug where there is half maximal growth; popmax is the theoretical maximum density of yeasts in the CSF; kkmax is the maximum rate of growth inhibition; C50k is the amount of drug where there is half maximal growth inhibition; and Hk is the slope function for growth inhibition.

The final model was assessed by: a visual inspection of the observed-versus-predicted concentration values plotted over time after the Bayesian step; the coefficient of determination (r^2) from the linear regression of the observed-versus-predicted values; and evaluation of the estimated bias (mean weighted error) and precision (adjusted mean weighted squared error). After fitting the model to the pharmacokinetic/pharmacodynamic data, the Bayesian posterior estimates for each rabbit were used to estimate the plasma and CSF concentration-time profiles for isavuconazole and the change in yeast CFUs over time in the CSF for each rabbit. CSF AUCs and the area under the $\log_{10}$ CFUs/mL in the

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Cryptococcus spp. in the CSF over time for each rabbit were calculated by integration from the simulated concentration-time profiles (on the last day of dosing for plasma) in Pmetrics.

Statistical comparisons were performed in GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA).

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All other authors have no conflicts of interest to declare.

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FIGURES

FIG 1 a-b Change in fungal burden in the rabbit. **(a)** Brain: All treatment groups (isavuconazonium sulfate 83.8 mg/kg and 111.8 mg/kg, and fluconazole 80 mg/kg) resulted in significant reductions in $\log_{10}$ CFU/g in the brain at the end of treatment compared with untreated rabbits ($P = 0.0003$; $P = 0.0002$; $P = 0.0034$, one-way ANOVA, Holm–Šidák's multiple comparisons test). There was no statistical difference between either isavuconazonium sulfate treatment group versus fluconazole ($P > 0.05$). **(b)** CSF: Significant changes in $\log_{10}$ CFUs/mL over time in CSF were demonstrated for all treatment groups (isavuconazonium sulfate 83.8 mg/kg and 111.8 mg/kg, and fluconazole 80 mg/kg) versus untreated rabbits ($P < 0.0001$; Tukey's multiple comparison test). Note: Not all animals survived to Day 14.

CSF, cerebrospinal fluid; ISAV, isavuconazonium sulfate; FLU, fluconazole.

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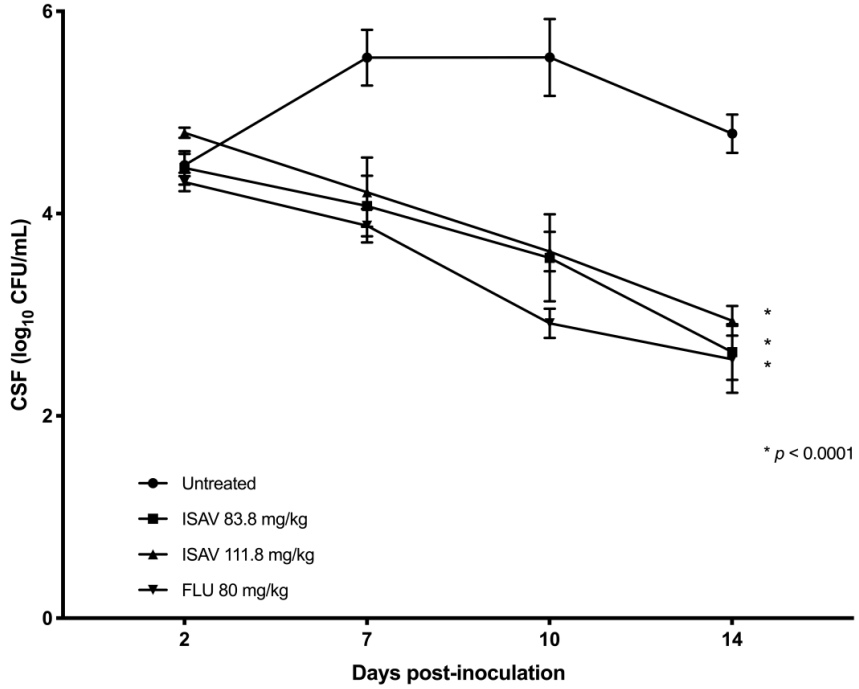
a.



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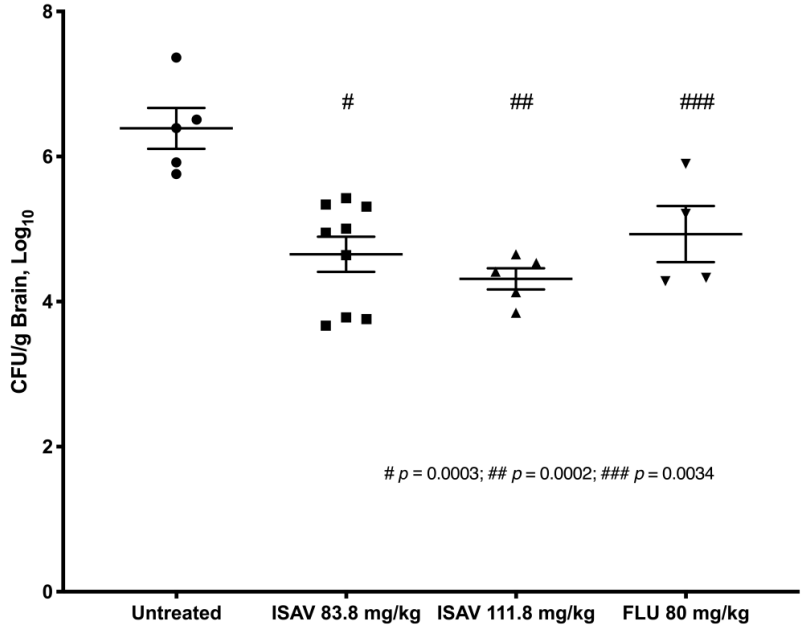

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467 **FIG 2 (a)** Observed versus median posterior predicted isavuconazole plasma
468 concentrations (mg/L) from the final model after the Bayesian step (r^2 = 0.841,
469 slope = 0.951 [95% CI 0.853 to 1.050], intercept = 0.366 [95% CI −0.018 to
470 0.751]). **(b)** Observed versus median posterior predicted isavuconazole CSF
471 concentrations (mg/L) from the final model after the Bayesian step (r^2 = 0.745,
472 slope = 0.958 [95% CI 0.79 to 1.13], intercept = 0.00198 [95% CI −0.00617 to
473 0.01010]). **(c)** Observed versus median posterior predicted $\log_{10}$ CFU/mL of CSF
474 from the final model after the Bayesian step (r^2 = 0.692, slope = 0.853 [95% CI
475 0.69 to 1.02], intercept = 0.577 [95% CI −0.0697 to 1.22]). Dotted line is line of
476 unity where observed equals predicted concentrations.
477 CSF, cerebrospinal fluid.
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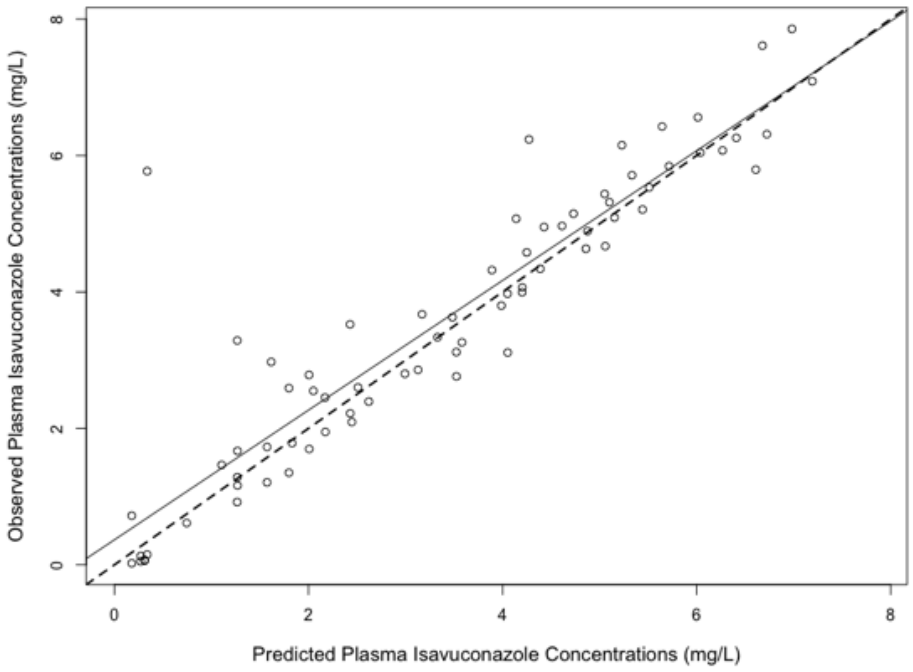
479 **FIG 2a**



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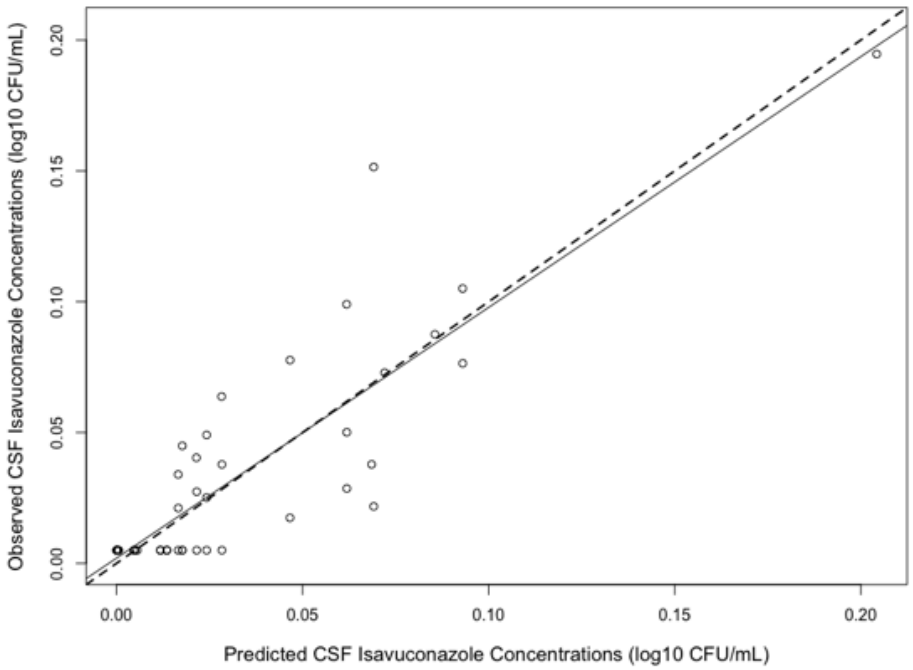
482 **FIG 2b**



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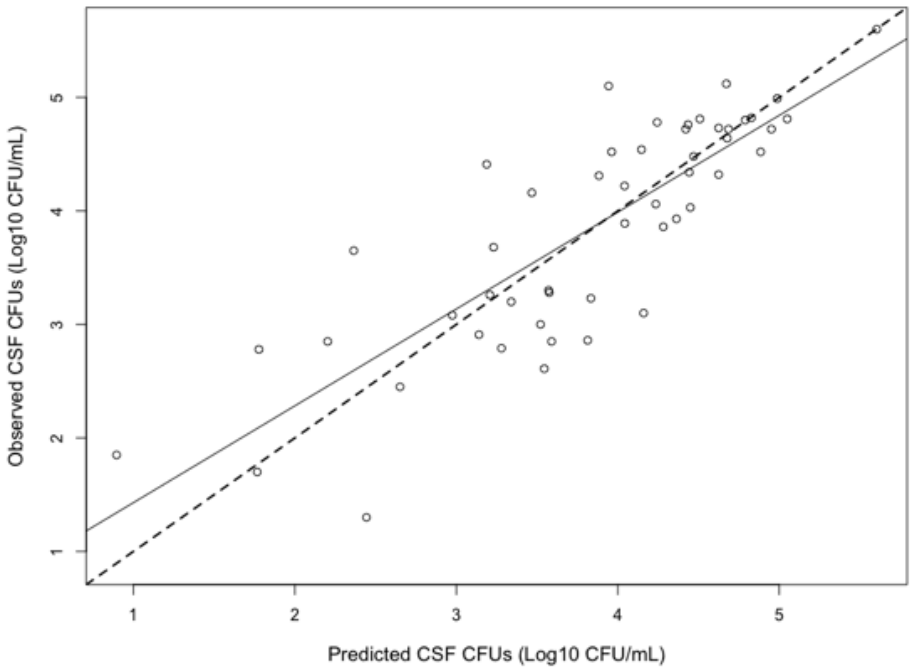
485 **FIG 2c**



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487 **Tables**

488

489 **TABLE 1** Mean and standard deviation observed isavuconazole concentrations

490 (mg/L) in the CNS by dose

	83.8 mg/kg	**111.8 mg/kg**
Brain	1.15 (±1.5)	1.31 (±0.96)
CSF	0.08 (±0.049)	0.05 (±0.028)
Ratio brain to plasma	0.69 (±0.69)	0.42 (±0.27)
Ratio CSF to plasma	0.044 (±0.044)	0.019 (±0.006)

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493 **TABLE 2** Mean and standard deviation values for each parameter estimated

494 from the rabbit population pharmacokinetic/pharmacodynamic-linked model

Parameter (units)	Mean	SD
Ka (h^{-1})	3.196	4.62
Cl/F (L/h)	2.639	2.26
Vc/F (L)	12.255	5.79
Vb/F (L)	165.876	51.75
Kcp (h^{-1})	17.942	9.82
Kpc (h^{-1})	20.135	9.83
Kcm (h^{-1})	13.959	13.52
Kmc (h^{-1})	16.593	9.00
Kgmax (log_{10} CFU/mL)	0.027	0.02
Hg	13.670	9.13
C50g (mg/L)	1.754	1.61
IC (log_{10} CFU/mL)	28,870.429	19,162.86
Kkmax (log_{10} CFU/mL)	11.168	5.19
Popmax (log_{10} CFU/mL)	409,294.206	449,097.00
Hk	3.697	2.66
C50k (mg/L)	1.928	1.42

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496 **TABLE 3** Mean plasma and CSF $AUC_{0–24}$ for each dose group and mean area

497 under the log_{10} CFUs/mL over time of *Cryptococcus* spp. in the CSF

	83.8 mg/kg	**111.8 mg/kg**
Plasma (mg*h/L)	50.83 (±33.302)	99.83 (±31.292)
CSF (mg*h/L)	2.87 (±2.013)	1.35 (±0.598)
Log_{10} CFUs/mL versus time	1,304.36 (±240.36)	1,379.01 (±273.89)
Decline log_{10} CFU/mL	1.78 (±0.69)	1.89 (±0.33)

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500 **TABLE 4** Plasma and CSF concentrations from two patients treated with

501 isavuconazonium sulfate

Dose	Serum (mg/L)	CSF (mg/L)	Ratio CSF/Plasma
Patient 1			
372 mg q24h	3.608	0.0296[a]	0.008
1,116 mg q24h	11.936	0.0917[a]	0.008
1,116 mg q24h	16.389	0.1312	0.008
744 mg q24h	13.924	0.0976[a]	0.007
558 mg q24h	11.749	0.109	0.009
558 mg q24h	9.371	N/A	N/A
372 mg q24h	6.227	N/A	N/A
Patient 2			
372 mg q24h	4.489	0.0228[a]	0.005
372 mg q24h	3.798	0.0405[a]	0.011

502 [a]Values < 0.1 mg/L are extrapolated and are not actual measured drug

503 concentrations.

504 N/A, not available; q24h, every 24 h.

505 Adapted from Everson et al. (14).

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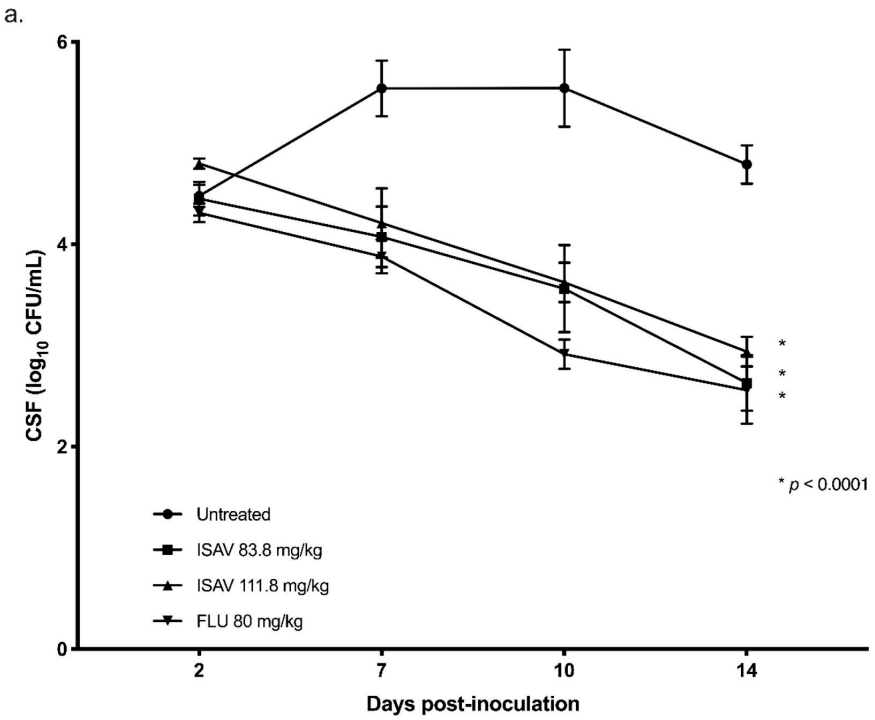

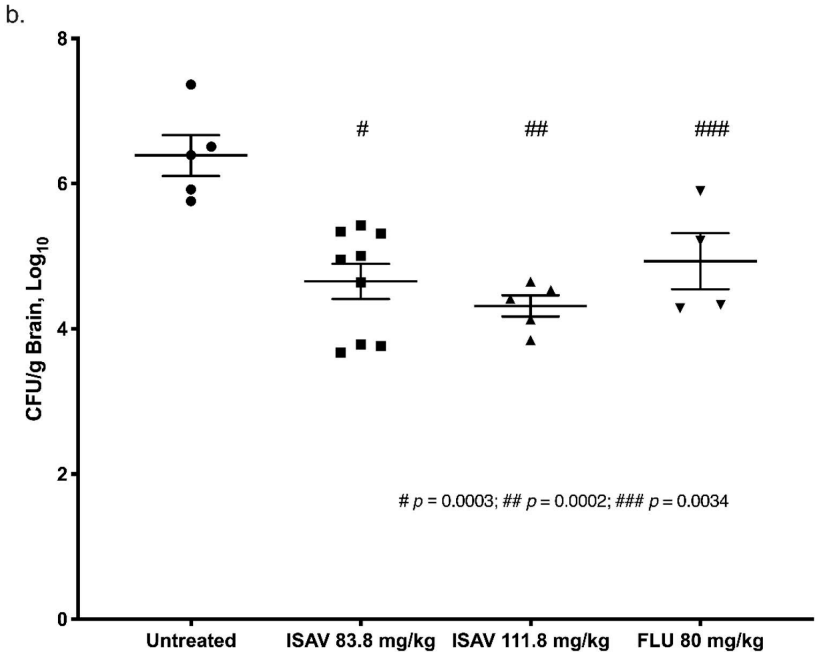

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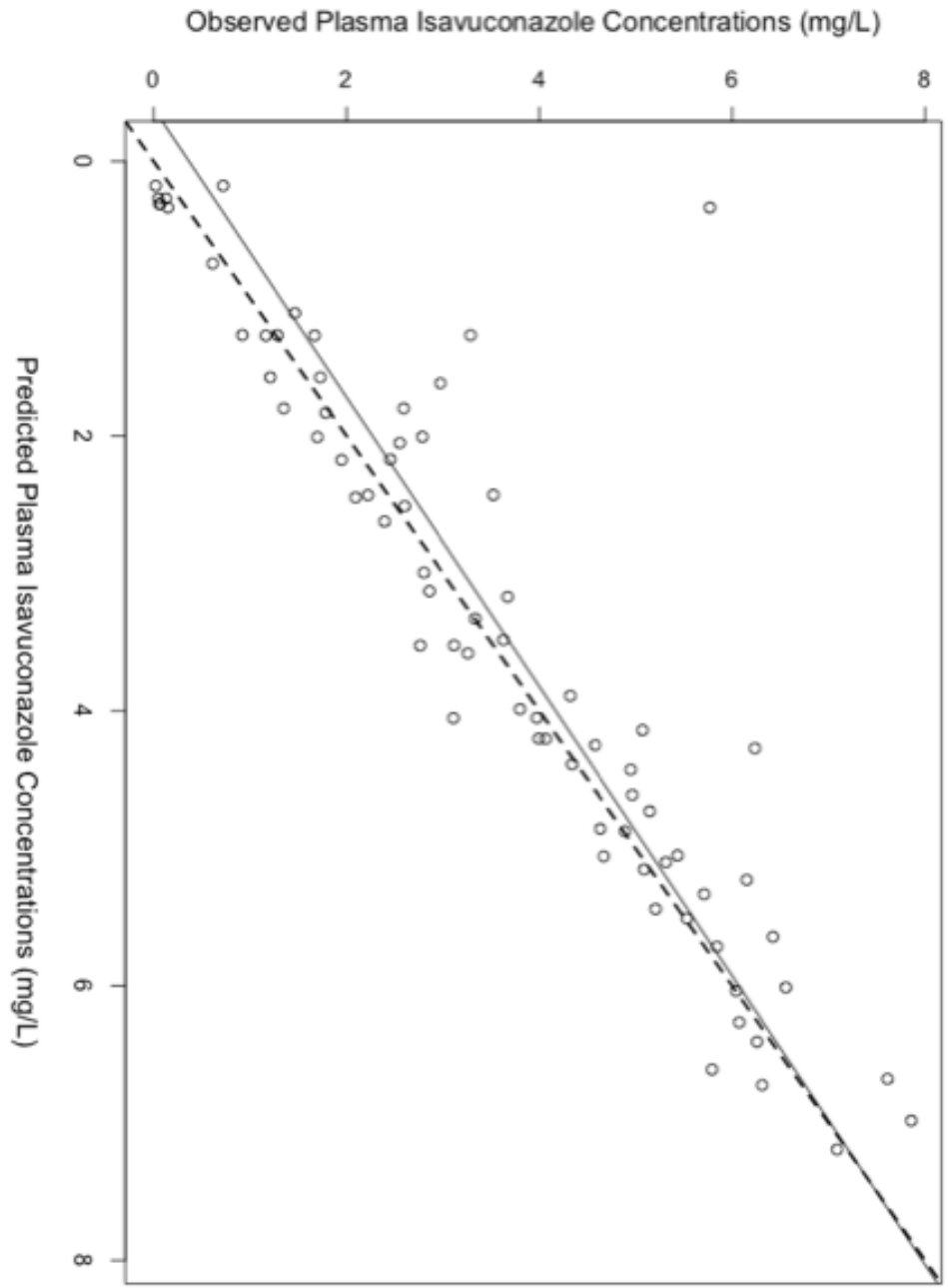

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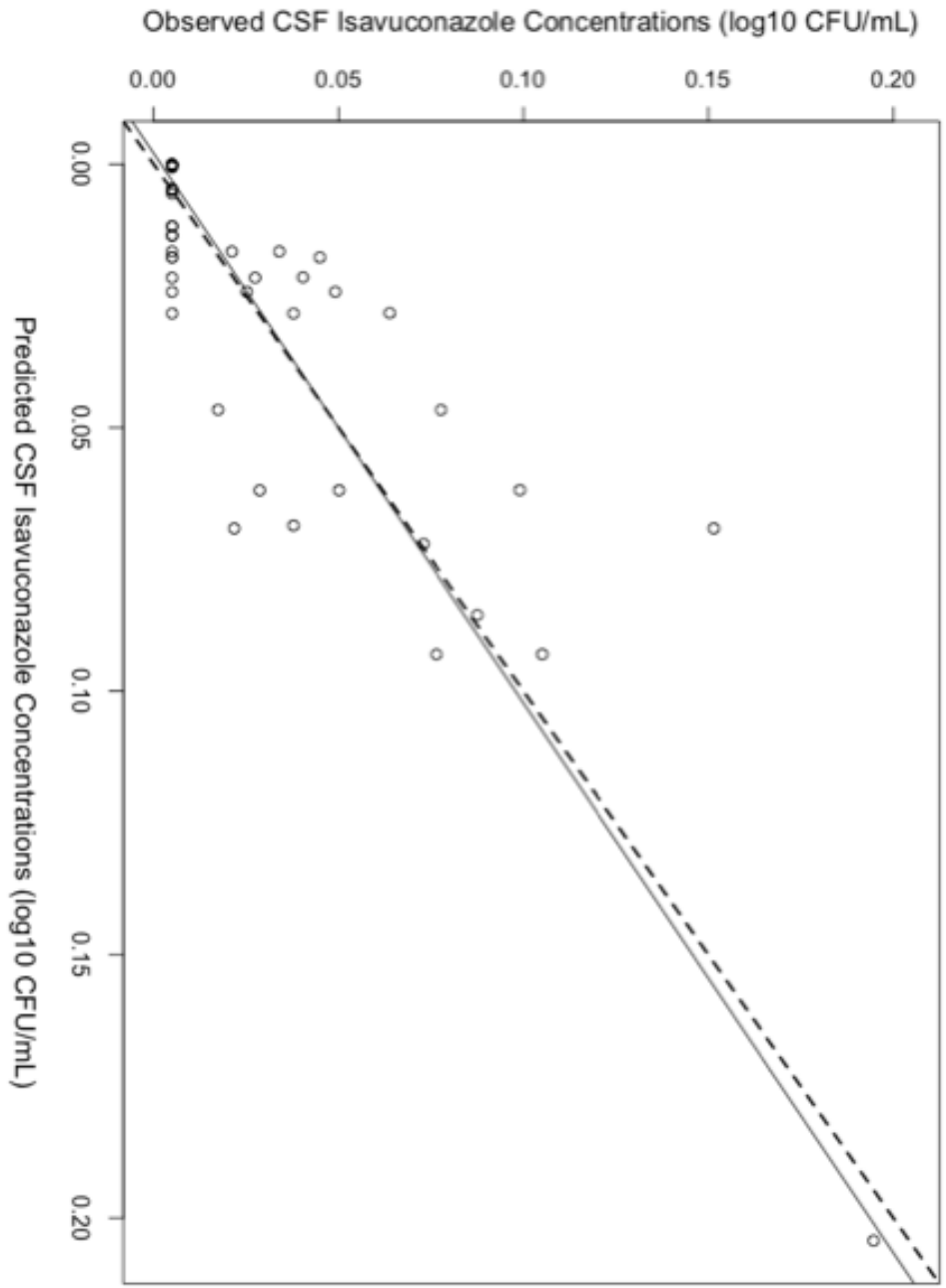

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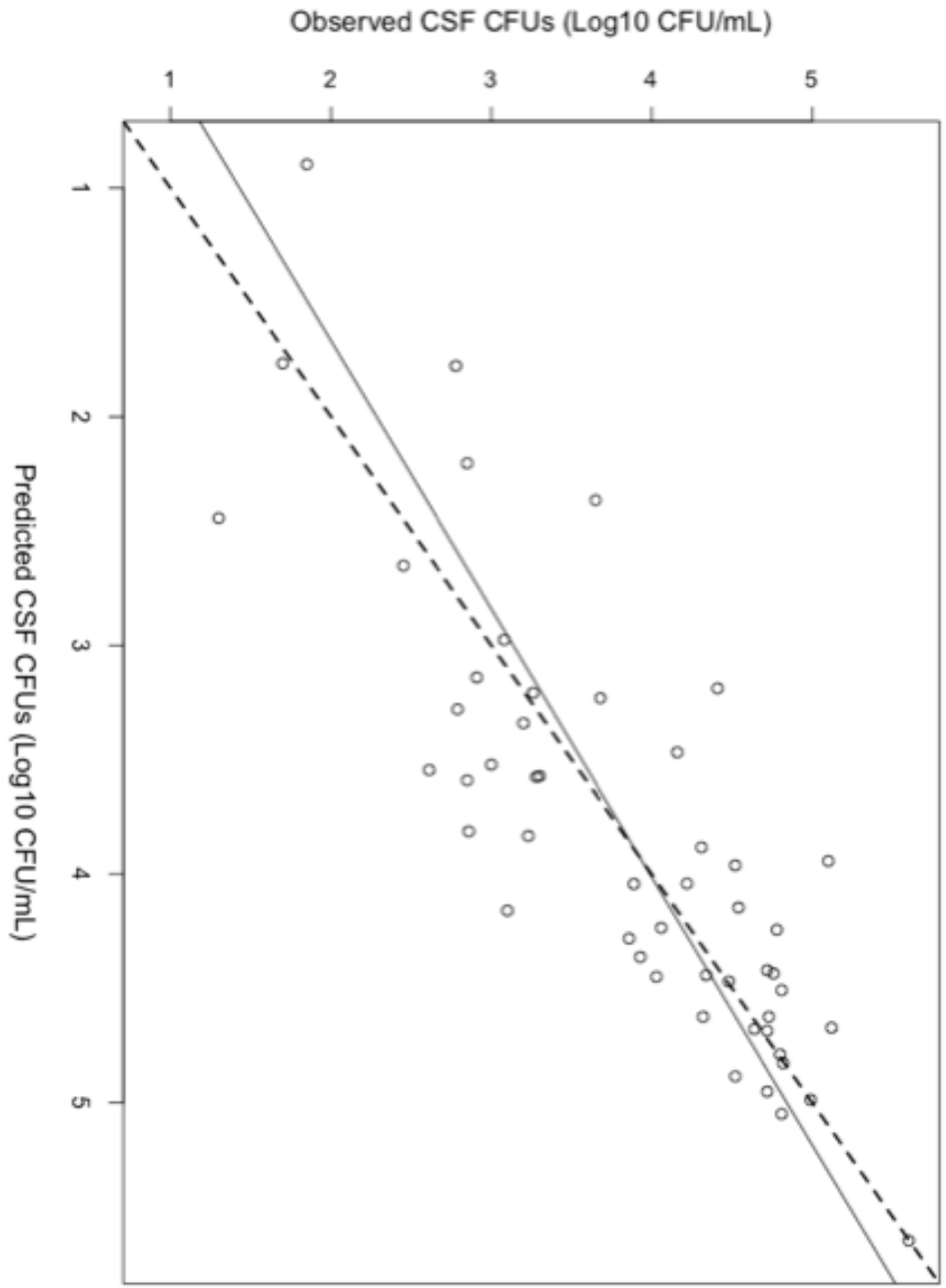

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