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Fluconazole Loading Dose Pharmacokinetics and Safety in Infants

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Keywords

candidiasis; fluconazole; infant; neonate; pharmacology

Invasive candidiasis is a leading cause of morbidity and mortality in critically ill infants.[1] Prompt administration of antifungal therapy can improve outcomes in candidemic patients.[2,3] Despite prompt therapy, 20% of young infants with candidiasis die as a result of invasive disease.[4,5]

Fluconazole is used frequently in infants for empiric antifungal therapy due to its excellent activity against *Candida* species, long half life, and low protein binding that allows for high cerebral spinal fluid penetration.[6] In adults, effective fluconazole pharmacokinetic/pharmacodynamic (PK/PD) indices for the treatment of candidiasis have been described.[7–10] A minimum (total drug) area under the curve (AUC) of 400 mg*hr/L ensures that the PK/PD index of AUC/minimum inhibitory concentration (MIC) stays >50 for *Candida* species with an MIC breakpoint ≤8 μg/mL.[11–13]

To reach the drug exposure target AUC of ≥400 mg*hr/L in critically ill infants, dosages of 12 mg/kg/day are recommended.[14] Because of the prolonged half life of fluconazole (24 hours), fluconazole dosing of 12 mg/kg/day might delay reaching desired target drug exposure concentrations for 5–7 days.[15] For many drugs with prolonged half life, a loading dose is a common strategy to achieve the therapeutic target after the first dose. A loading dose (1600 mg~25 mg/kg) of fluconazole is commonly used in adults with candidemia on the first day of therapy.

This loading dose strategy is recommended for adults with candidemia by the Infectious Disease Society of America.[16,17] Despite frequent use of fluconazole in infants, the PK and safety of a loading dose in infants are not known. The purpose of this study was to

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determine whether a fluconazole loading dose of 25 mg/kg would safely achieve the therapeutic target (AUC of 400 mg*hr/L) after the first day of therapy in young infants at risk of invasive candidiasis.

MATERIALS AND METHODS

Study design

This was a prospective, single-center, open-label PK and safety trial of a fluconazole loading dose in infants <60 days of age at Duke University Medical Center in Durham, NC. We recruited subjects from the Pediatric Intensive Care Unit, the Pediatric Cardiac Intensive Care Unit, and the Neonatal Intensive Care Unit. Subjects were given an intravenous loading dose (25 mg/kg administered over 2 hours via a syringe pump) followed by maintenance therapy (12 mg/kg/day over 1 hour). Infants received maintenance therapy for 4 days unless there was a positive culture for *Candida* from normally sterile body fluid, in which case infants were to be given additional antifungal therapy for confirmed invasive candidiasis at the discretion of the primary medical team. Results of all cultures obtained from sterile body fluids while receiving fluconazole were recorded.

Subjects

Hospitalized infants between 48 hours and 60 days of age at risk for invasive fungal infection with recent blood cultures (<72 hours of study entry) were eligible for enrollment. Infants were excluded from participation if there was a history of recent (<5 days) fluconazole exposure; hepatic dysfunction (AST or ALT >250 U/L); renal dysfunction (serum creatinine >1.3 mg/dL or receiving renal replacement therapy); history of hypersensitivity or severe vasomotor reaction to any triazole; or concomitant use of cyclosporine, tacrolimus, or azithromycin.

The institutional review board of Duke University Medical Center and the review board of the Pediatric Pharmacology Research Unit Network approved this study. We obtained written informed consent from the parent or primary legal guardian of all subjects. ClinicalTrials.gov ID: NCT00797420 (http://clinicaltrials.gov/ct2/show/NCT00797420).

Sample Collection and Preparation

We obtained 6–8 plasma samples (200 μL each) following the loading dose for the determination of fluconazole concentration at the following time points after the end of the infusion: 0–30 minutes, 2–4 hours, 6–12 hours, and 18–24 hours; and peak and trough sampling at doses 3 and 5 (0–4 hours before dose and 2–6 hours after dose). Samples were collected into EDTA microcontainers and not taken from the same site as the fluconazole administration. Plasma was separated by centrifugation (3000 rpm for 10 minutes within 4 hours of the blood draw), manually aspirated, and transferred into polypropylene tubes removed within 30 minutes. To supplement timed plasma samples, infants had up to 6 scavenged plasma samples from residual discarded blood (<72 hours old) obtained as part of routine clinical care. Timed and scavenged plasma samples were both frozen at −20°C and were later transferred for storage at −70°C within 7 days until analysis.

Analytic Procedures

Plasma fluconazole concentrations were determined using a validated liquid chromatography-tandem mass spectrometry assay.[15,18] The lower limit of quantification was 0.01 μg/mL; intraday and interday coefficients of variation were ≤11.5% at concentrations ranging from 0.01–10 μg/ml.

Pharmacokinetic and Statistical Analysis

A non–linear-regression analysis according to a 1-compartment open model after intravenous infusion administration was used to describe the time-concentration data for each subject using WinNonLin v. 5 (Pharsight Co., St. Louis, Missouri). Even though a sparse sampling study design was followed, it has been shown that a 1-compartment PK model appropriately describes the PK of fluconazole in infants.15 PK parameters including volume of distribution (Vd) and clearance (CL) were computed. The model fit was evaluated using several model-fitting criteria including successful minimization; goodness of fit as assessed by the Akaike Information Criterion; diagnostic plots; and precision of parameter estimates. $AUC_{0–24}$ was computed by the linear trapezoidal method using the predicted data. Median predicted fluconazole trough concentrations at 24, 48, 72, and 96 hours were compared by visual inspection and descriptive statistics.

Fluconazole PK data for the study cohort were examined by standard descriptive statistics (i.e., mean, standard deviation, median, and interquartile range [IQR]). The primary outcome was the number of infants achieving a therapeutic fluconazole $AUC_{0–24}$ ≥400 mg*hr/L within 24 hours following the loading dose.

The unit of observation for this analysis was the infant. We evaluated fluconazole CL versus serum creatinine fitting a linear regression model to the data. Continuous variables were described using summary statistics. Categorical variables were described using counts and percentages. We used STATA 10 (College Station, Texas) to perform the statistical analysis.

Safety Assessment

Physical examinations and laboratory examinations, including chemistry, were done at baseline and following the loading dose. The primary safety outcome of interest was hepatotoxicity as defined by elevation of liver transaminases >250 U/L. For this reason, all subjects had liver transaminases measured a minimum of 1 time during the duration of the study, if not done per standard of care by the primary medical team. Adverse events were recorded from the time of the fluconazole loading dose administration until 72 hours following the last dose of the study drug. All new adverse events or pre-existing conditions aggravated in severity were recorded and their severity and relationship to the loading dose were documented. Safety analyses included all patients who received a loading dose of fluconazole. All adverse events were recorded, and the safety data were summarized descriptively.

RESULTS

Patients

Ten infants were enrolled from November, 2008, through February, 2010. PK data from 8 infants, including 57 plasma samples, were evaluable among those infants receiving a loading dose of fluconazole. Two infants were excluded from the PK analysis. One infant was omitted because of incomplete dosing as a result of receiving standard dosing in lieu of a loading dose of fluconazole. The second infant was omitted due to the lack of confirmation of dosing and PK sampling times.

The median age, gestation age at birth, and birth weight for all subjects enrolled were 16 days (IQR 13–32), 37 weeks (35–38), and 2.8 kg (2.0–3.1), respectively (see table, Supplemental Digital Content 1, http://links.lww.com/INF/A680). Eight of 10 infants (80%) were receiving mechanical ventilation at the time of study drug administration. One infant was receiving extracorporeal membrane oxygenation (ECMO) support. There were no subjects with positive blood cultures. Two infants had fungal urinary tract infections

(*Candida tropicalis* and yeast not further speciated). *Chryseobacterium meningosepticum* was isolated from lung tissue in 1 infant.

Pharmacokinetics

Data from 57 plasma concentrations (6–8 per patient) and 8 patients were included in the PK analysis. Fifty-four out of 57 (95%) were timed samples processed according to the PK protocol, and 3/57 (5%) were scavenged samples from discarded clinical blood specimens.

A plot of the individual plasma concentration data after loading dose administration is shown in Supplemental Digital Content 2, http://links.lww.com/INF/A681 (figure). The data conformed well to the 1-compartment model with zero-order infusion; the observed minus predicted sum of square of residuals was small and randomly distributed around zero. The median (IQR) of the elimination rate constant (kel) obtained from the model fit was 0.02 (0.01–0.03) (Table 1).

In this small cohort of infants, fluconazole clearance was highly variable with a range of 9–27 mL/kg/h (Table 1). Other PK parameters are summarized in Table 1. After the administration of a single 25-mg/kg loading dose of fluconazole, 5 of the 8 infants (63%) achieved the therapeutic target $AUC_{0–24}$ >400 mg*hr/L, and all infants achieved a 24-hour trough concentration >8 ug/mL Table 1, Figure Supplemental Digital Content 2, http://links.lww.com/INF/A681). The median $AUC_{0–24}$ achieved by the study participants was 479 mg*hr/L (IQR 347–496). The lowest fluconazole exposures were observed in 2 infants with severe anasarca. The third infant with subtherapeutic fluconazole exposures was being supported by ECMO. The median $AUC_{0–24}$ of the 7 infants excluding the 1 supported by ECMO was 493 mg*hr/L (range 271–499). The highest observed $AUC_{0–24}$ was in an infant with an elevated serum creatinine (1.2 mg/dL) and an inverse relationship between fluconazole CL and serum creatinine was observed (see Figure, Supplemental Digital Content 3, http://links.lww.com/INF/A682). After multiple doses, fluconazole accumulation was apparent as evidenced by an increase in median predicted trough concentrations at 24, 48, 72, and 96 hours (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/A681).

Safety

Overall, a single loading dose of fluconazole (25 mg/kg) was well tolerated among study participants. Two of the 8 infants (25%) experienced an adverse event. All of the adverse events were felt to be likely unrelated to the study drug by the investigator. One infant, who had a history of both complex congenital heart disease and arrhythmias, had a brief episode (<30 seconds) of ventricular tachycardia >24 hours after the loading dose. Another infant, who was receiving ECMO support, had transiently worsening renal insufficiency felt to be secondary his clinical condition and ECMO support. There were no clinically significant elevations noted in liver transaminases or signs of hepatotoxicity. None of the subjects had elevated (>250 U/L) liver transaminases during the study period. The median baseline AST and ALT were 27 U/L (IQR 22–32) and 13 U/L (10–14), respectively. Following the loading dose, the median AST and ALT were 21 U/L (16–42) and 21 U/L (9–56), respectively.

DISCUSSION

Young infants at risk for invasive candidiasis should receive antifungal therapy at doses designed to achieve the target therapeutic concentration rapidly, which is essential in the treatment of severe, life-threatening, fungal infections.[3,19–21] A loading dose of twice the usual daily dose of fluconazole is recommended for adults with candidemia on the first day

of therapy to obtain plasma concentrations close to steady-state. 22,23 Current fluconazole dosing in young infants is based on limited PK data11,14,15,24 and requires 5–7 days to achieve the target therapeutic concentration in young infants.14,25 We conducted the first clinical trial evaluating a fluconazole loading dose in infants as a strategy to more rapidly achieve the target therapeutic concentration.

The majority of the infants in our study achieved the therapeutic target $AUC_{0–24}$ >400 mg*hr/L, and all achieved 24-hour trough concentrations >8 ug/mL following the loading dose. These results are concordant with population PK and simulation studies of a fluconazole loading dose previously conducted in young infants14 and confirm that a fluconazole loading dose is required to achieve the therapeutic target after the first dose. Drug accumulation was observed following the loading dose, which suggests that a prolonged dosing interval (i.e., every 48–72 hours) may be adequate in this population.

Several subjects in our study, however, did not achieve the therapeutic target. One of these subjects was receiving ECMO support during study drug administration. The appropriate fluconazole dose in critically ill patients requiring ECMO is unknown. The ECMO circuit is known to substantially alter the PK of drugs, resulting in changes in drug elimination and Vd.26–30 The cardiovascular instability and renal insufficiency of patients requiring ECMO support can further affect the PK of drugs in this population.31 Our infant who received ECMO support demonstrated lower fluconazole exposures in spite of worsening renal function (serum creatinine 1.3 mg/dL). This finding suggests that the ECMO circuit may be responsible for part or even the majority of fluconazole clearance in this subject. In addition, the dosing weight for this patient was estimated on the basis of the subject's most recent weight because of the limitations associated with weighing patients while connected to the ECMO circuit. The estimated dosing weight is likely an underrepresentation of the patient's true weight given the anasarca that is associated with ECMO, and this difference likely contributed to the low fluconazole exposure. To further define the effects of the ECMO circuit on the PK of fluconazole, a study evaluating the PK of fluconazole in patients under ECMO support is underway.

The other patients who did not achieve the therapeutic target were critically ill with severe anasarca, including 1 subject with an open sternotomy following cardiac surgery and 1 subject on high-frequency jet ventilation. There were similar limitations for these subjects in obtaining an accurate dosing weight. The combination of an inaccurate dosing weight and severe anasarca leading to increased Vd likely contributed to these subjects not achieving the therapeutic target AUC. The subject who did not receive a loading dose would have likely reached the therapeutic target if a loading dose was given due to the linear kinetics observed with fluconazole.

None of the infants enrolled in our study reached an $AUC_{0–24}$ >800 mg*h/L, which is the recommended therapeutic target for immuno-compromised adults with candidemia.17 This highlights the need for a minimum loading dose of 25 mg/kg along with future simulation and clinical trials of the PK and safety of higher loading doses in infants. Subtherapeutic fluconazole concentrations commonly achieved with current dosing strategies may be contributing to the high mortality and morbidity of candidiasis in infants.

While rare but serious hepatic toxicity has occurred in patients taking fluconazole, this toxicity does not appear to be related to dosage or total drug exposure and is generally reversible on discontinuation of therapy.32 The package insert for Diflucan® (fluconazole) includes the following warning: "Diflucan has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of Diflucan-associated hepatotoxicity, no obvious relationship to total

daily dose, duration of therapy, sex, or age of the patient has been observed. Diflucan hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy."7

The association of fluconazole with hepatotoxicity was our primary safety concern. In the present study, a fluconazole loading dose was well-tolerated and did not result in hepatotoxicity or elevation in liver transaminases in this small cohort of patients. Larger studies evaluating the safety of fluconazole in children further support our findings. Among 562 children (0–17 years of age) who received fluconazole (1–12 mg/kg/day), only 3 (0.5%) developed hepatotoxicity. This adverse event could have been attributed to concomitant use of other therapeutics.32

Our prospective clinical trial confirms that a fluconazole loading dose of 25 mg/kg achieves the desired therapeutic target in the most critically ill infants. In special clinical circumstances, such as patients supported by ECMO, patients with anasarca, or the immuno-compromised host, a higher fluconazole loading dose may be required. The critically ill nature of this study population is a strength of the study because it is this group of children and infants who are at the highest risk of invasive candidiasis. While a loading dose achieved the therapeutic target $AUC_{0–24}$ >400 mg*hr/L in the majority of infants, none of the subjects reached an AUC>800 mg*hr/L, which is currently recommended for critically ill candidemic adults. Prospective confirmatory studies of the PK and safety of the loading dose strategy in preterm infants and older infants along with efficacy trials are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Pharmacokinetic Parameters

Subject	Age (days)	Serum Creatinine	Clearance (mL/kg/h)	Vd (mL/kg)	Half life (h)	Kel (h^{-1})	AUC_{0-24} ($mg^{*}hr/L$)
1	6	1.0	27	785	19.9	0.050	493
2	13	1.3	14	1441	73.4	0.013	350
3	14	0.8	12	1522	91.4	0.010	338*
4	14	0.5	18	1021	39.1	0.025	466
5	19	1.2	9	1081	79.4	0.012	493
6	36	0.5	21	711	23.8	0.042	598
7	55	0.3	23	882	27.2	0.036	506
8	59	0.2	14	1635	81.2	0.012	271
Median	17	0.7	16	1051	56	0.02	479
(IQR)	(14–41)	(0.4–1.1)	(13–21)	(858–1461)	(26–80)	(0.01–0.03)	(347–496)

*Infant 3 was supported by extracorporeal membrane oxygenation.