Published in final edited form as:
Curr Med Chem. 2012 ; 19(27): 4617–4620.

Fluconazole pharmacokinetics and safety in premature infants

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Introduction

Invasive candidiasis (IC) is common in extremely premature infants and causes substantial morbidity and mortality.[1, 2] Up to 30% of infants with IC die,[3–5] and nearly 60% of survivors suffer from neurodevelopmental impairment.[2] Risk factors for IC include lower gestational age, exposure to broad spectrum antibiotics, and presence of central venous catheters.[6] Appropriate dosing of antifungals is needed to prevent death and IC-related morbidities in this population.

The most commonly used first line antifungals to treat IC in infants are amphotericin B deoxycholate and fluconazole.[7] Amphotericin B deoxycholate is associated with nephrotoxicity in adults[8, 9], and has limited pharmacokinetic (PK) and dosing data in the premature patient population. Fluconazole has potential therapeutic advantages over amphotericin B deoxycholate. Fluconazole has an excellent safety profile and is effective at treating >90% of *Candida* isolates causing IC in premature infants.[6] Additionally, fluconazole has excellent cerebral spinal fluid (CSF) penetration[10] and is excreted, nearly unchanged, in the urine. As a result, the use of fluconazole as an alternative for treatment against IC has been increasing in neonatal intensive care units NICU) over the past 10 years.[11, 12]

Fluconazole, a synthetic triazole, is a highly selective inhibitor of lanosterol 14-α-demethylase, a fungal cytochrome P450 enzyme[13]. This enzyme is responsible for converting lanosterol to ergosterol. This loss of normal sterols in the cell wall induces fungal cell lysis and death, with minimal effect on mammalian cells. Fluconazole is approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in adults for the treatment of vaginal candidiasis, oropharyngeal and esophageal candidiasis, and cryptococcal meningitis. Additionally the EMA includes indications for invasive candidiasis, dermatomycosis, coccidiomycosis, and onychomycosis. Fluconazole is labeled by the EMA for use in term newborn infants and children aged 0–17 years for the treatment of mucosal candidiasis, IC, cryptococcal meningitis, and prophylaxis of IC in immunocompromised children. Though not formally indicated for use, the FDA label states

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that fluconazole is efficacious in children 6 months through 13 years for the treatment of oropharyngeal candidiasis.[13–15]

In this article, we will review the fluconazole PK and safety in adults and children, followed by a literature review of the PK and safety in premature infants.

Fluconazole PK and Safety in Adults

Fluconazole PK is well described in the adult population. The volume of distribution (V) is similar to that of body water (0.7 L/kg). Fluconazole has low plasma protein binding (11%)[16] and is renally cleared as predominately unchanged drug, with metabolism accounting for only a minimal component of clearance (CL), 0.23 mL/min/kg.[17] Systemic exposure has a linear relation to dose, and plasma half-life (t½) is 30 hours. The recommended dosing for peripheral infections is 100 – 200 mg every 24 hours, and dosing for systemic infections in neutropenic patients range from 400 – 800 mg daily.[12]

A 24-hour area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio model is predictive of treatment efficacy.[17, 18] Experimentally, an AUC/MIC ratio >50 is >70% efficacious for both mucosal and invasive infections. When treating *Candida* infections, an MIC breakpoint of ≤8 μg/mL requires a minimum fluconazole AUC of 400 mg*h/L for effective treatment.[12, 19, 20]

Fluconazole is generally well tolerated in adults. Elevated liver transaminases have been documented, but are not dose-dependent and typically resolve with discontinuation of treatment.[16, 21] Fluconazole also rarely causes a nondescript rash.[13]

Fluconazole PK and Safety in Children

Fluconazole PK in children is less well described. In 101 children[22], stratified by age (3 months – 2 years; 2 – 12 years; 12 – 16 years), the PK paramaters changed during growth and development. The V in the youngest group was higher than in adults but was similar to adults in the oldest group (0.95 L/kg and 0.7 L/kg). The half-life (t½) was similar across all three pediatric age groups (21.4 h, 22.7 h, 21.4 h). The shorter t½ (67% that of adults) and larger V (133% that of adults) observed in this study suggested that an increased dose (6–12 mg/kg body weight) for children > 3 months of age should be used for IC.[22]

Fluconazole has been shown to be safe in children. The largest review in children (n=562, age 0–17 years) of published data on fluconazole safety showed that at doses of 1–12 mg/kg/day, 11% of children experienced side effects and 3% discontinued fluconazole therapy due to side effects. The most commonly reported effects were gastrointestinal (7.7%), and rash (1.2%). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase elevations were reported in 4.9%, 2.7%, and 2.3% of patients, respectively.[23]

Fluconazole PK in premature infants

We performed a literature review of the PK of fluconazole in premature infants. We searched Medline, with the following search terms: fluconazole AND (pharmacokinetics OR pharmacodynamics) AND (preterm OR premature OR ELBW (extremely low birth weight) OR VLBW (very low birth weight) OR lbw (low birth weight)) AND limits (newborn – 1 month). This returned 68 abstracts, and 2 authors (KT and ML) determined which were most appropriate. Five manuscripts were reviewed.[16–20]

Saxen et al. first described the PK of fluconazole in 12 premature infants receiving fluconazole prophylaxis.[24] The study enrolled infants on postnatal day 1, median gestational age (GA) of 27.4 weeks (25.9 – 29.4 weeks) and median weight 912 g (750g – 1100g), and

administered an intravenous dose of 6 mg/kg every 72 hours for 2 weeks. Fluconazole PK parameters changed rapidly during the first 2 weeks of life. The V increased from 1.18 to 2.25 L/kg, the CL increased from 0.011 L/kg/h to 0.031 L/kg/h, and the t½ decreased from 88.6 to 55.2 hours (Table 1).[24, 25]

Nahata et al[26] examined fluconazole PK in 6 premature infants, median GA of 30 weeks (26 – 40 weeks) and median postnatal age of 51 days (23 – 81 days). All 6 infants received 6 mg/kg of enteral fluconazole, and 2 later received 6 mg/kg of intravenous fluconazole. The clearance per percent bioavailability (CL/F) ranged from 0.16 to 0.29 ml/min/kg. The peak serum concentration (Cmax) ranged from 6 to 13.5 μg/mL; and the AUC (0–∞) ranged from 340 to 636 μg*h/mL; and were comparable to IV fluconazole (Table 1). This study provided preliminary evidence that enteral and IV fluconazole may achieve comparable serum concentrations in premature infants.

Wenzl et al.[27] determined the PK of enteral fluconazole in 3 premature infants, mean GA of 27 weeks (24 – 29 weeks), with *Candida* sepsis. The infants were given enteral fluconazole (4.5 – 6 mg/kg/day) and PK samples were obtained on the 20th day of treatment. The V ranged from 1.21 to 1.88 L/kg, the t½ ranged between 27 to 45 hours, and the AUC ranged from 131 to 233 μg*h/mL) (Table 1).[27] This provided evidence that the dosing was too low in this population.

Recognizing the need for PK studies in premature infants, investigators in the Pediatric Pharmacology Research Unit (PPRU) designed and implemented a population PK study. Fifty-five premature infants were enrolled in a multicenter fluconazole PK study.[24] In the resulting population PK model, investigators found that CL is directly related to GA and serum creatinine, and doubles during the first month of life (Table 1). Infants with a serum creatinine >1.3 mg/dL had > 70% reduction in CL. The population PK model was then externally validated with previously published PK data.[24] The authors used Monte Carlo simulations to calculate target exposures for different prophylaxis and therapeutic dosing based on gestational age. They demonstrated that, during the first 90 days of life, in an infant < 30-weeks GA, a fluconazole dose of 12 mg/kg/d would result in an efficacious exposure (AUC of >400 μg*h/L and an AUC/MIC >50 for *Candida* strains with an MIC <8 μg/mL) in >90% of the patients.[28] In addition, given the prolonged t½ (30 – 50 hours) in this population, steady state was not reached until after day 5 of treatment. Therefore, a loading dose (25 mg/kg) was recommended to achieve the target AUC day 2 of therapy.

Fluconazole loading dose may be needed for premature infants

A fluconazole loading dose approach is commonly used among critically ill adults to reach fluconazole steady state concentrations early in the treatment course.[29–31] A recent study evaluated the PK of a 25 mg/kg fluconazole loading dose in critically ill infants, median age of 16 days (interquartile rage [IQR], 13 – 27), GA of 37 weeks (IQR 25 – 38 weeks) and 2.8kg (IQR 2.0 – 3.1kg). Over 60% (5/8 infants) reached the desired therapeutic target (AUC >400 mg*h/L). Of the 3 failures, 2 had severe anasarca, and the third subject was supported on an extracorporeal membrane oxygenation (ECMO) circuit.[32] These factors likely influenced their lower AUC observed. It is likely that premature infants need a loading dose as well, and further investigation is warranted.

Safety in Premature Infants

Relatively few studies have examined the safety of fluconazole in the premature infant. Most collected data are derived from studies assessing the role of fluconazole as prophylaxis for IC. Five randomized control trials, consisting of 726 premature infants, evaluated fluconazole's effect on hepatotoxicity.[33–37] Of these trials, only two studies demonstrated

stastistically significant increases in AST and ALT, though none of these were considered to be clinically significant. These values normalized after discontinuation of fluconazole. Another study evaluated fluconazole hepatotoxicity when being used as prophylaxis in ELBW infants, and compared liver function tests to historical controls. They found an increased risk of conjugated hyperbilirubinemia (43% compared to 9%, P<0.001), while on therapy.[38] These values also normalized after discontinuation of fluconazole.

Neurodevelopmental impairment (NDI) is an important long-term outcome for many premature infants, and it is important to determine if therapeutics have an adverse effect on NDI. Eighty-six ELBW premature infants were treated with placebo or fluconazole of 3 mg/kg with increasing dosing frequency (initially dosed every 72h, then progressing to daily dosing) for 6 weeks. The subjects receiving fluconazole were compared to those receiving placebo at 8 to 10 years for differences in neurodevelopmental adaptive abilities, behavior, and quality of life; and the two groups were found to be equivalent.[39, 40]

In the five phase I studies examining PK of fluconazole in the premature infant, there were no adverse drug reactions reported. Adverse events of fluconazole in premature infants are mild and self-limiting, similar to those children and adults. Fluconazole appears to be safe to use in the premature infant population.

Fluconazole prophylaxis

In premature infants, *Candida* species progress from colonization to invasive disease. In the neonatal intensive care unit (NICU), up to 60% of very low birth weight (VLBW) infants are colonized with *Candida* in the first month of life.[36] Prophylaxis of high-risk patients to prevent a systemic fungal infection has been investigated with fluconazole, in four randomized controlled trials.[33, 34, 36, 37] A meta-analysis of this data demonstrates fluconazole to be safe and effective at preventing both colonization and infection with *Candida* [relative risk 0.48 (95% CI 0.31, 0.73); number needed to treat (NNT): 11 (95% CI 7, 33)].[41] These studies were conducted in centers with a high incidence of *Candida*, and it is uncertain if these results would be replicated in low or moderate incidence sites. A randomized, controlled trial of fluconazole prophylaxis in infants <750 g birth weight has recently been completed (NCT# 00734539); results are forthcoming.

Summary

IC is common in extremely premature infants and accounts for substantial morbidity and mortality. Collectively, the PK data reported in this unique, critically ill population demonstrates that in order to achieve therapeutic concentrations, fluconazole dosing in premature infants should be 12 mg/kg/day. Moreover, a loading dose (25 mg/kg) may be required to rapidly achieve appropriate steady state concentrations. These findings differ substantially from observations in older children and adults and reinforce the need for the study of the dosing and safety of drugs used in this vulnerable patient population. Fluconazole appears to be safe to use in this population, with only minimal hepatobiliary effects that reverse upon discontinuation of therapy. Fluconazole may also have a role in prophylaxis of IC, especially in centers with high incidence of IC. PK profiles of therapeutics used in infants must be described using phase I trials, as the PK cannot be extrapolated from adult data.

Abbreviations

ELBW	Extremely low birth weight
VLBW	Very low birth weight

PK	Pharmacokinetics
PD	Pharmacodynamics
GA	Gestational age
V	Volume of distribution
t½	Terminal half life of elimination
Cmax	Maximum serum concentration

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Table 1

Pharmacokinetic studies of fluconazole in premature infants

Study	N	GA (weeks)	Dose (mg/kg)	BW (g)	t½ (hr)	CL (L/kg/hr)	V (L)	Cmax (μg/mL)	AUC (μg*hr/L)
Saxen et al.[24]	12	25–29	6	750–1100	5–89	0.011–0.031	1.18–2.25	3.7 – 17.8	not reported
Nahata et al.[26]	6	26–40	6	not reported	not reported	0.010 –0.017	not reported	6 – 13.5	340–636
Wenzl et al.[27]	3	24–29	4.5–6	not reported	35	not reported	1.43	6.8 – 11.9	175.4
Wade et al.[42], [28]	55	23–40	3–12	451–7125	not reported	*	*	not reported	not reported

N = Number of subjects
GA = Gestational age (weeks)
BW = Birth weight (g)
t½ = Terminal half life of elimination (hours)
CL = Clearance (ml/min/kg)
V = Volume of distribution (L/kg)
Cmax = Maximum serum concentration (μg/ml)
AUC = area under the curve (ug*hr/ml)

* These results were reported as a formula, based on the population PK model, to calculate PK parameters