Early Human Development 90S1 (2014) S87–S90

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Fluconazole prophylaxis in preterm infants: a multicenter case-controlled analysis of efficacy and safety

David A. Kaufman [a,*], Amy Morris [b], Matt J. Gurka [c], Barry Kapik [b], Seth Hetherington [d]

[a] Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, USA
[b] Inhibitex, Atlanta, GA, USA
[c] Department of Biostatistics, West Virginia University, Morgantown, WV, USA
[d] Icagen, Inc. Durhum, NC (SH), USA

ARTICLE INFO

Keywords:
Fluconazole prophylaxis
Preterm infants
Candida
Antifungal
Safety

ABSTRACT

Background: Fluconazole prophylaxis has demonstrated efficacy in single and multicenter randomized controlled trials without side effects or emergence of resistance. Additional evidence based on incidence of invasive *Candida* infections, multicenter data, resistance, and safety is desired.
Methods: We conducted a case-control analysis of efficacy and safety of fluconazole prophylaxis from a multicenter database from a neonatal infection study that included 2017 infants <1250 grams from 95 NICUs. Infants receiving intravenous antifungal prophylaxis were pre-identified during enrollment in the parent study. For each infant receiving antifungal prophylaxis (case), three infants not receiving antifungal (controls) were matched by birth weight (± 50 g), by gestational age (±1 week), gender, and study site.
Results: Fluconazole prophylaxis was administered to 127 patients [754±163 g birth weight (BW) and 25.4±1.7 weeks gestational age (GA)] and were compared with 399 control patients (756±163 g BW and 25.5±1.8 weeks GA). Invasive *Candida* infection occurred in 0.8% (1 of 127) infants who received fluconazole prophylaxis compared with 7.3% (29 of 399) of matched controls ($p = 0.006$). *Candida* bloodstream infection occurred in 0.8% (1 of 127) fluconazole prophylaxis infants compared with 5.5% (22 of 399) of matched controls ($p = 0.02$). There were no differences in late-onset sepsis due to gram-positive or gram-negative organisms, focal bowel perforation, necrotizing enterocolitis, cholestasis, or overall mortality.
Conclusion: Fluconazole prophylaxis is safe and efficacious in preventing invasive *Candida* infections. Even in NICUs with a low incidence of invasive *Candida* infections, antifungal prophylaxis for high-risk infants is a proven and safe opportunity for infection prevention in these patients.

1. Introduction

Fluconazole prophylaxis for the prevention of invasive *Candida* infections in high-risk preterm infants has been studied in single center and multicenter randomized controlled trials (RCTs) as well as several single center observational studies [1–3]. There is A-I evidence supporting antifungal prophylaxis in high risk preterm infants confirmed by meta-analyses, Cochrane reviews, the American Academy of Pediatrics (AAP) and the Infectious Diseases Society of America (IDSA) [4–6].

While fluconazole prophylaxis has demonstrated efficacy, safety including long term neurodevelopmental outcomes, and lack of emergence of fungal resistance; more safety information during the same time period is desired from multicenter studies [7–10]. This information is critical as safe prevention is needed in preterm infants, especially those <1000 grams with invasive *Candida* infections, in which death or neurodevelopmental impairment occurs in 73% [11–13].

A multicenter study of late-onset sepsis in preterm infants 500–1250 grams from 95 NICUs defined a priori those infants who received antifungal prophylaxis with fluconazole [14]. This created the opportunity for analysis of the effect of fluconazole prophylaxis on outcomes. In addition to examining the efficacy of fluconazole prophylaxis from a large multicenter database, adverse events, morbidities and mortality could be analyzed in infants who received prophylaxis compared with birth weight and gestational age matched controls.

2. Methods

Data were retrospectively collected from the database of a prospective, placebo-controlled, randomized Phase III clinical trial of INH-A21 (Veronate®; Inhibitex, Inc.), an anti-staphylococcal immune-globulin [14]. The study was approved by local Institu-

* Corresponding and reprint request author: Dr. David A. Kaufman, MD, Division of Neonatology, Department of Pediatrics, Box 800386, University of Virginia School of Medicine, Charlottesville, VA 22908, USA. Tel.: +1 434-924-9114; fax: +1 434-924-2816.
E-mail address: dak4r@virginia.edu (D.A. Kaufman).

0378-3782/$ – see front matter

tional Review Boards and was registered at www.clinicaltrials.gov (NCT00113191). A complete study methodology has been published [14]. This study was performed between May 2004 and January 2006 across 95 centers in the United States and Canada. Infants with a birth weight between 500 and 1250 grams were eligible for enrollment if they were expected to survive at least four weeks and required intravenous access for 10 to 14 days. Infants were excluded from the trial for any of the following: evidence of sepsis (culture proven or clinical signs), severe congenital anomalies, congenital immunodeficiency, significant fluid overload or depletion, or a serum creatinine >1.6 mg/dL. Infants were also excluded if they had received any immune-globulin product or were placed on prophylactic antibacterial antibiotics for prevention of nosocomial or central line-related infection. Antifungal prophylaxis was permitted and not an exclusion criteria.

The database of INH-A21 Phase III study was utilized to analyze the impact of the use of prophylactic antifungals on invasive *Candida* infections. INH-A21 is an intravenous immune globulin derived from donors with high titers of antibody to surface adhesins of *Staphylococcus epidermidis* and *S. aureus*, and patients were randomized to receive 750 mg/kg INH-A21 or saline placebo [14]. Infants were not randomized for antifungal or fluconazole prophylaxis. Patients were also stratified into two birth weight groups: 500–900 g and 901–1250 g. Patients had data collected until study day 70, or less if discharge, transfer to another institution, or death occurred sooner. Concomitant medication use was collected during the study. The use of antifungals for prophylaxis was specifically designated a priori on the case report form, but the decision to use antifungals was at the discretion of the neonatal clinicians. INH-A21 did not have an effect on invasive *Candida* infections or any infection-related outcomes [14]. Infants enrolled in study at 3–5 days with demographic and fluconazole information collected from birth and subsequent data collected prospectively.

We conducted a case-control analysis. We performed the analysis this way as 90% of the invasive *Candida* infections and also 90% of the patients who received fluconazole prophylaxis were <1000 grams, while only 64% of the total 2017 patients were <1000 grams. For each infant receiving antifungal prophylaxis (case), three infants not receiving antifungal (controls) were matched by birth weight (±50 g), and when possible, by gestational age (±1 week), gender, and study site. This resulted in 82% of controls being matched by birth weight, gender and gestational age, with 17% of the controls included matching by site. Differences between these two groups of infants on rates of infection and morbidities were performed using a Cochran-Mantel-Haenszel Chi-squared test, controlling for birth weight group. Adverse events and serious adverse events were analyzed using Fisher's exact test.

While antifungal prophylaxis with fluconazole was captured, the decision to use, timing, dosage, and length of prophylaxis was at the discretion of the neonatal clinicians. Post-hoc survey of principal investigators was sent out after the study completion for further information on the dosage and schedule administered, and patient selection criteria for fluconazole prophylaxis.

Serious adverse events defined as any event leading to death, life-threatening events, or events requiring procedural or surgical intervention were also compared between groups.

3. Results

A total of 2017 infants were enrolled in the study. Fluconazole prophylaxis was used in 17 of 95 sites (18%) during the study. There were 133 patients captured as receiving antifungal prophylaxis from the case report forms and initially matched to 399 controls. Of the 133 patients, 127 were confirmed to have received fluconazole prophylaxis. Fluconazole prophylaxis was administered for a median (interquartile range) of 38 (20–48) days.

Table 1
Patient demographics and risk factors.

	Fluconazole prophylaxis	Matched control	*P value*
No. of patients	127	399	
Demographics			
Birth weight	754±163	756±163	1.00
Gestational age	25.4±1.7	25.5±1.8	0.27
Male gender	48%	48%	1.00
Vaginal delivery	31%	29%	0.71
Apgar score at 5 minutes	8 (0–9)	7 (0–9)	0.01
Maternal antibiotics <24 hours prior to delivery	68.4%	55.4%	0.01
Maternal race			
Caucasian	60.2	61.7	0.62
Black	35.3	33.6	
Asian	2.3	1.5	
Hawaian	1.5	1	
Native American	0.8	0.5	
Hispanic	16.5%	13%	0.16
Risk factors			
Early-onset sepsis [a]	3.0%	3.3%	0.88
NEC ≥ stage 2	12.8%	10.5%	0.27
Focal bowel perforation	7.5%	5.0%	0.28
3rd generation cephalosporin use	47%	43%	0.43
Carbapenem use	8.3%	4.8%	0.13
Fluoroquinolones	3.8%	1.3%	0.07

Mean ± sd, median (range). NEC, necrotizing enterocolitis.
[a] Positive culture at baseline.

The majority of demographic characteristics including birth weight and gestational were similar between groups (Table 1). Maternal use of antibiotics within 24 hours of delivery (68.4% vs. 55.4%) and Apgar score at five minutes (8 vs. 7) were higher among the prophylaxis group.

3.1. Invasive Candida infections

Blood, urine, or cerebrospinal *Candida* infection occurred in 1 of 127 (0.8%) fluconazole prophylaxis patients compared to 29 of 399 (7.3%) of the control infants ($p = 0.006$) (Table 2). One (0.8%) of 127 infants in the prophylaxis group compared to 22 of 399 matched controls (5.5%) developed candidemia ($p = 0.02$). The one fluconazole prophylaxis patient developed *Candida parapsilosis* candidemia and was a 24-week, 712 gram infant who survived to discharge. This *C. parapsilosis* isolate was susceptible to fluconazole with a minimum inhibitory concentration (MIC) of 1.

3.2. Safety

The incidence of cholestasis was similar between both groups. There were no differences in late-onset sepsis due to gram-positive or gram-negative organisms, necrotizing enterocolitis (NEC), or focal bowel perforation. There was also no difference in overall mortality, overall serious adverse events, serious adverse events leading to death, or non-fatal serious adverse events between cases and controls.

3.3. Dosing survey

Fluconazole prophylaxis dosing varied little between centers. Post study, centers were surveyed on dosing and guidelines for fluconazole prophylaxis that was used during the study and 80 of 95 sites responded. Twelve of 80 (15%) centers had guidelines for fluconazole prophylaxis. The most common practice was the administration of intravenous fluconazole prophylaxis at a dose of 3 mg/kg either twice weekly or more frequently in infants <1000 g until they no longer had intravenous access or up to 6 weeks. Other centers used fluconazole prophylaxis while needing a