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Clinical Pharmacology of Fluconazole in Neonates: Effects and Pharmacokinetics

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Abstract

Fluconazole is commonly used both to prevent and to treat invasive neonatal Candida albicans infection. This drug is a potent, selective, triazole inhibitor of the fungal enzymes involved in ergosterol synthesis. It is largely excreted unchanged in the urine. In infants with a birth weight <1,500 grams, fungal infection is approximately 3% to 4%. Up to 30% of infants with invasive candidiasis die. Penetration into the cerebral spinal is good. While high-dose systemic exposure of 400 mg/day in the first trimester of pregnancy can produce serious fetal abnormalities a single dose of 150 mg of fluconazole does not produce fetal abnormalities. The fluconazole exposure target AUC of ≥400 µg.h/ml should be reached and a dosage of 12 mg/kg/day is recommended. However, to reach the desired fluconazole concentration a loading dose of 25 mg/kg of fluconazole is used in patients with candidiasis on the first day of therapy. The half-life of fluconazole ranges from 25.5 to 88.6 hours while adults it is 32 hours. In prematures, the half-life of fluconazole is 88.6, 67.5 and 55.2 hours, in the first day, in the first week and in the second week of life, respectively. The clearance of fluconazole ranges from 0.27 to 0.52 ml/min/kg and the adults it is 0.27 ml/min/kg. The distribution volume of fluconazole ranges from 1.1 to 2.4 l/kg and in adults it is 0.60 l/kg. The aim of this study is to review the effects and pharmacokinetics of fluconazole in neonates.

Key Words: Effects, Fluconazole, Neonates, Pharmacokinetics.

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1- INTRODUCTION

Fluconazole, first approved as an anti-fungal in France and the UK in 1988, is now established word wile as a leading systemic antifungal drug (1). Incidence of systemic fungal infections, especially among the very low birth infants (<1500 grams) is approximately 3% to 4% (2, 3).

Invasive candidiasis is common in extremely premature infants and causes substantial morbidity and mortality (4, 5). Up to 30% of infants with invasive candidiasis die (6-8). Risk factors for invasive candidiasis include lower gestational age, exposure to broad spectrum antibiotics, and presence of central venous catheters (9).

Systemic candidiasis is difficult to diagnose, but not rare in colonized ill infants. The isolation from blood should never be ignored. Unfortunately, blood cultures may take days to reveal evidence of infection and can be misleadingly negative. The presence of budding years or hyphae in freshly voided urine should lead to an immediate search for further evidence of infection.

Candida is the most important agent of fungal infections (10). Fluconazole is a triazole antifungal agent that is widely used in the nursery. It is available in both intravenous and oral formulation, and is active against most of the fungal pathogens that require treatment when retrieved from culture samples in neonatal intensive care units. Fluconazole is a potent, selective inhibitor of the fungal enzymes involved in ergosterol synthesis. This drug is reasonable effective against most Candida species, other than Candida krusei and Candida glabrata. It is of value in the treatment of cryptococcal infection, although treatment needs to be sustained for several weeks (11). Penetration into cerebral spinal fluid is good. While high-dose systemic exposure (400 mg/day) in the first trimester of pregnancy can produce serious abnormalities, there are, as yet, no reports of teratogenicity with a single 150 mg dose in the first trimester or with topical or oral use later in pregnancy (12). Fluconazole is increasingly used in the treatment of systemic Candida albicans infection. This drug is less toxic and at least as effective as amphotericin B. Liver function tests sometimes show a mild self-correcting disturbance, and rashes can occur, but serious drug eruptions have only been seen in immunodeficiency patients. The half-life in neonates ranges from 25.5 to 88.6 hours; it is 20 hours throughout infancy and childhood. In adults it is 32 hours (13). There is no good reason to give amphotericin B as well as high-dose fluconazole, but there is evidence that effective treatment of all Candida species with a minimum inhibitory concentration of ≤ 8 μg/ml requires a higher dose than many reference texts currently quote (14).

Manzoni et al. (15) observed that Candida colonization affected 54 of 336 infants (16.1%). Baseline (i.e. detected <3rd day of life) colonization affected 16 (4.7%), and acquired 38 (11.4%) of the 54 colonized preterms studied. Infants with baseline colonization had significantly higher birth weight (1,229$\pm$28 grams vs. 1,047$\pm$29 grams, P=0.01) and gestational age (30.2$\pm$2.7 weeks vs. 28.5$\pm$2.6 weeks, P=0.01) and were significantly more likely to limit progression from colonization to invasive Candida infection when fluconazole prophylaxis was instituted (21.6% vs. 42.7%, P=0.009). Isolation of Candida parapsilosis was significantly more frequent in infants with acquired colonization. Infants with baseline and acquired colonization differ for demographic characterization and for their response to fluconazole prophylaxis. This information may be useful for targeting more accurate management strategies for these two different groups of colonized preterms in the neonatal intensive current unity.

To reach the fluconazole exposure target area under the curve (AUC) of ≥400 µg.h/ml in critically ill infants, the recommended dosage of fluconazole is 12 mg/kg/day. Because of the prolonged half-life of fluconazole, fluconazole dosing of 12 mg/kg/day might delay reaching desired drug exposure concentrations for 5 to 7 days. A loading dose of 25 mg/kg of fluconazole is commonly used in patients with candidemia on the first day of therapy (16).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and PubMed as search engines; December 2015 were the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keyword AND "Fluconazole effects neonate" keyword AND "Fluconazole pharmacokinetics neonate" keyword AND "Infants" keyword) were used to search for the relevant literature. In addition, the books Neonatal Formulary (11) and NEOFAX by Young and Mangum (17) were consulted.

2-3. Prophylactic use in neonates

Age under 2 weeks: give 6 mg/kg of fluconazole on day 1 and then a further 6 mg/kg every third day. Age 2-4 weeks: give 6 mg/kg of fluconazole on day 1 and then a further 6 mg/kg every second day (11).

2-4. Treatment of invasive candidiasis

Age under 2- week: give 6-12 mg/kg of fluconazole every third day. Age 2-4 weeks: give 6-12 mg/kg of fluconazole every second day. Age 4- week to 1 year: give 6-12 mg/kg of fluconazole every 24 hours. A loading dose of 25 mg/kg has sometimes been recommended and shortens the time to achieving therapeutic levels. Double the dosage interval after the first two doses if there is renal failure (11).

2-5. Monitoring

Serum fluconazole concentrations are not routinely followed. Assess renal function. Follow aspartate aminotransferase, alanine aminotransferase, and direct bilirubin, especially in patients on higher doses. Periodic complete blood count for eosinophilia can be used (17).

3- RESULTS

3-1. Effects of fluconazole in neonates

Fluconazole prophylaxis was administered to 127 infant patients (754±163 g birth weight and 25.4±1.7 weeks of gestation) and were compared with 399 control infants (756±163 g birth weight and 25.5±1.8 weeks of gestational age) (18). 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 was no difference in late-onset sepsis due to gram-positive organisms, focal bowel perforation, necrotizing enterocolitis, cholestasis, or overall mortality. Fluconazole prophylaxis is safe and efficacious in preventing invasive Candida infections. Maede et al. (19) conducted a comparative clinical study to evaluate the prophylactic effects of micafungin and fluconazole on the incidence of fungal infection in extremely low-birth weight infants who were born at a gestational age less than 26 weeks and weighted less than 1,000 grams. With a combination of enteral administration of miconazole (6 mg/kg/day), fluconazole and micafungin were administered intravenously at a dose

of 5 mg/kg/day and 3 mg/kg/day, respectively. The prophylaxis was classified as a failure when fungal infections were identified within 21 days after birth. The prophylaxis was successful in 7 of 18 cases (39%) in the fluconazole group and 15 of 21 cases (71%) in the micafungin group, indicating that the success rate was significantly higher in the latter group. Micafungin was superior to fluconazole as prophylaxis against fungal infections in extremely low-birth weight infants. Kaufman et al. (20) observed that fluconazole prophylaxis for the prevention of invasive Candida infections is safe in extremely low birth weight infants and does not appear to be associated with any long-term adverse effects on neurodevelopment and quality of life at 8 to 10 years of life.

Fluconazole prophylaxis is associated with cholestasis in extremely low-birth weight infants. Bhat et al. (21) administered fluconazole twice a week for up to 6 weeks and compared this with infants who received the frequent dosing schedule (every 72 hours for first 2 weeks, every 48 hours for next 2 weeks and every 24 hours for the final 2 weeks). The two groups were compared for baseline demographics, risk for candidiasis, the rate of invasive fungal infection and the incidence and severity of cholestasis. The low frequency dosing regimen of fluconazole prophylaxis is effective in preventing invasive fungal infection in extremely low-birth weight infants. The severity of cholestasis was decreased with the low frequency dosing schedule.

Extremely low-birth weights were divided into 2 groups. Fluconazole were administered to 163 infants and 99 infants were the controls. Frequency of invasive fungal infection was 7.1% in the control group versus 1.8% in the fluconazole group (P=0.045). There was no difference in the frequency of cholestasis between the control and fluconazole groups. Prophylactic administration of fluconazole to all extremely low-birth weight infants was associated with significantly decreased in invasive fungal infection without associated adverse effects (22). There is strong evidence that systemic fluconazole prophylaxis reduces the incidence of systemic fungal infections, with a trend towards reduction in mortality. Fluconazole use is sometimes associated with cholestasis and there are theoretical concerns as well that prophylactic fluconazole will select for fluconazole-resistant organisms and non-albicans Candida infections. Nystatin is effective in preventing fungal infections and, at the same time, is inexpensive and well tolerated. Oral nystatin prophylaxis is inexpensive, effective and nontoxic and should be used in infants of birth weight less than 1,500 grams. Systemic fluconazole which is more toxic and may select for resistant fungi, is probably only indicated when the rate of fungal infection remains high despite introducing measures targeting known risk factor for fungal infections (23).

Weitkamp et al. (24) aimed to evaluate if limiting fluconazole prophylaxis to targeted highest risk infants effectively prevents invasive fungal infections, has no undesired side effects and limits unnecessary drug exposure. A total of 86 extremely low-birth weight infants were included in the study, 44 in the no-prophylaxis group and 42 in the prophylaxis group. In the targeted prophylaxis group, no invasive fungal infections were observed as compared to nine infants with invasive infections in the no-prophylaxis group (P=0.004). No significant adverse effects were recorded. Targeting the highest risk infants reduced the number of infants <1,000 grams requiring prophylaxis from 80 to 42 (48% reduction) with no preventable infection missed. Provider compliance was 91% following implementation of this protocol

through the computerized physician order entry system using a standardized order set. Targeting the highest risk infants for fluconazole prophylaxis through computerized physician order entry can effectively prevent invasive fungal infections and limit drug exposure with no unwanted side effects.

Kaufman et al. (25) tested the hypothesis that twice weekly prophylactic dosing of fluconazole prevents invasive candidiasis without promoting resistant Candida species in high-risk preterm infants. Twice weekly dosing of prophylactic fluconazole can decrease Candida colonization and invasive infection, cost, and patient exposure in high-risk preterm infant weighing <1,000 grams at birth. These authors speculate that lower and less frequent dosing of fluconazole may delay or prevent the emergence of antifungal resistance.

Kaufman et al. (26) evaluated the efficacy of prophylactic fluconazole in preventing fungal colonization and invasive infection in extremely-low-birth-weight infants. 50 infants randomly assigned to fluconazole and 50 control infants were similar in terms of birth weight, gestational age at birth, and base-line risk factors for fungal infection. During the six-week treatment period, fungal colonization was documented in 30 infants in the placebo group (60%) and 11 infants in the fluconazole group (22%), P=0.002. Invasive fungal infection with positive growth of fungal isolates from the blood, urine, or cerebral fluid developed in 10 infants in the placebo group (20%) and none of the infants in the fluconazole group (P=0.008). The sensitivities of the fungal isolates to fluconazole did not change during the study, and no adverse effects of the fluconazole therapy were documented. Prophylactic administration of fluconazole during the first six weeks of life is effective in preventing fungal colonization and invasive fungal infection in infants with birth weights of less than 1,000 grams.

Kicklighter et al. (27) determined whether prophylactic fluconazole for the first 28 days of life results in a decreased incidence of candidal colonization in very-low-birth infants. One hundred and three infants were enrolled within 72 hours of life with rectal cultures performed on the day of randomization, as well as day of life 7, 14, and 28. Those infants with a birth weight of <1,250 had additional cultures on 35, 49, and 56 days of life. Infants were randomized to receive either fluconazole (6 mg/kg) or placebo on the day of randomized. Subsequent doses were given every 72 hours until day of life 7 and then every 24 hours until day of life 28. Medication was given either intravenously or by feeding tube once the infant had been gavage feeding for a 48-hour period without feeding intolerance. The infants who received fluconazole (n=53) and placebo (n=50) shoved no statistical differences in the major risks known to increase the changes of candidal septicemia in the very-low-birth-weight infant. Rectal colonization by candidal species was detected in 8 of the 53 fluconazole-treated infants (15.1%) and in 23 of the 50 infants treated with placebo (46%). Fluconazole significantly reduced rectal colonization from day of life 14 throughout day of life 56 in all infants with a birth weight of <1,250 grams, and from day of life 14 throughout day of life 56 in all infants with a birth weight of 1,250 to 1,500 grams. There was no increase in species of Candida noted for their intrinsic resistance to fluconazole, and there was no statistically significant difference in the minimal inhibitory concentrations to fluconazole for Candida albicans isolates in either group at any period. Prophylactic administration of fluconazole to the very-low-birth weight infant in the first 28 days of life is safe and results in a decreased

risk of rectal colonization by candidal species.

A total of 24 neonates and infants, aged from 2 days to 10 months, received treatment with intravenous fluconazole for microbiologically documented or presumed fungal infection. The mean fluconazole dosage was 6 mg/kg/day and the mean duration of therapy was 25 days (range 5-72 days). Efficacy was evaluated in neonates with proven fungal infections, as documented by the presence of pathogen at baseline. A positive clinical response was achieved in 23 of the 24 clinically evaluable patients (96%); eradication of the fungal organism was also achieved in 23 of the 24 evaluable patients (96%). Adverse effects occurred in two patients (8%) but therapy was not discontinued in either patient, the present results confirm the efficacy and safety of fluconazole in the treatment of neonates and infants with severe fungal infections (28). Narang et al. (29) evaluated the role of fluconazole in the management of neonatal systemic candidiasis in 23 neonates with a mean birth weight of 1,590±533 grams and with a mean gestational age of 32.3±3.1 weeks. Fungal sepsis was diagnosed at a mean age of 14.3±7.9 days. Candida albicans (43.5%), Candida tropicalis (21.7%), Candida guillermondii (13%) and Candida krusei (8.7%) were the species isolated. Fluconazole was effective in 82.3% cases with no side effects. Four resistant cases were Candida parapsilosis (n=2), Candida albicans (n=1) and Candida guillermondii (n=1) and there were three deaths, all resistant cases though one death was unrelated to candidemia. Fluconazole is a safe and effective drug for neonatal systemic candidiasis.

Fluconazole prophylaxis appears to be tolerated for use in premature infants. Reduction in the incidence of invasive candidiasis is observed even when prophylaxis is limited to infants with multiple risk factors. Centers with a low incidence of invasive candidiasis may benefit from fluconazole prophylaxis. Significant short-term and long-term toxicity and increases in fluconazole-resistant organisms have not been observed with fluconazole use in the intensive care nursery (30).

Invasive candidiasis can cause significant neurodevelopmental impairment even if it is successfully treated. Preterm infants are at risk for hematogenous Candida meningoencephalitis owing to increased permeability of the blood-brain barrier, so antifungal treatment should have adequate central nervous system penetration. Amphotericin B deoxycholate, lipid preparations of amphotericin B, fluconazole, and micafungin are first-line treatment of invasive Candida. Fluconazole prophylaxis reduces the incidence of invasive candidiasis in extremely premature infants, but its safety has not been established for this indication, and as yet, the product has not been shown to reduce mortality in neonates. Targeted prophylaxis may have a role in reducing the burden of disease in this vulnerable population (31).

Gardner et al. (32) aimed to evaluate the effectiveness of prophylactic fluconazole on the incidence of fungal infections and to assess whether hospital-acquired fungal infection is associated with increased in-hospital mortality in pediatric cardiac patients requiring extracorporeal membrane oxygenation. Extracorporeal membrane oxygenation was deployed 801 times in 767 patients. After exclusion criteria were applied, 261 pediatric patients supported for cardiac indication were studied. Fungal infection (blood, urine, or surgical site) occurred in 12% of 127 patients receiving fluconazole prophylaxis versus 22 (16.4%) of 134 without antifungal prophylaxis (P=0.02). Using a multivariate logistic regression model, the absence of fluconazole prophylaxis was

associated with an increased risk of fungal infection (P=0.016). In a multivariate logistic regression model for in-hospital mortality, the presence of fungal infection was associated with increased odds (P=0.072). Children with cardiac disease supported with extracorporeal membrane oxygenation who acquire fungal infections have increased mortality. Routine fluconazole prophylaxis is associated with lower rates of fungal infections in these patients. Manzoni et al. (33) studied 465 neonates who weighed <1500 grams at birth. Fluconazole prophylaxis was administered to 225 infants whereas 240 infants did not receive fluconazole. Overall fungal colonization was significantly (P<0.05) lower in neonates who received fluconazole until the 30th day of life (24%) than in infants who did not received fluconazole (43.8%). Systemic fungal infection incidence was lower in the infants who received fluconazole (10 of 225; 4.4%) than in the infant who did not receive fluconazole (40 of 240; 16.7%). Reduction of both colonization and systemic fungal infection in neonates who received fluconazole was greater in neonates who did not receive fluconazole. Rate of progression from colonization to infection was significantly lower in fluconazole treated infants. Crude mortality rate attributable to Candida species was 1.7% (4 of 240) in infants not treated with fluconazole versus 0% (0 of 225) in treated infants. Overall mortality rate (any case before hospital discharge) was similar in the two groups (11.2% vs. 10.6%), but in colonized infants (n=159), it was significantly (P<0.05) lower in treated infants (3.7% vs. 18.1). The incidence of natively fluconazole-resistant fungal species did not increase over the years, and patterns of sensitivity to fluconazole remained the same. No adverse reaction related to fluconazole occurred. Prophylactic fluconazole significantly reduces the incidence of colonization and systemic infection by Candida species in very-low-birth weight neonates and decreases the rates of progression from initial colonization to massive and systemic infection. All very-low-birth weight neonates may benefit from fluconazole prophylaxis.

Standard neonatal systemic antifungal therapy with amphotericin B and flucytosine can be associated with toxicity, drug resistance and the need for prolonged venous access. There is consequently a need for alternative treatment options. Wainer et al. (34) assessed the efficacy and safety of fluconazole in the treatment of systemic neonatal fungal infections. Clinical and microbiologic cure was achieved in 12 of 19 (63%) infants treated. One additional infant received prior amphotericin B therapy and is included for assessment of side effects. One infant with Torulopsis glabrata infection failed treatment. Six infants died of Gram-negative bacterial infection and other intercurrent medical problems. Fluconazole appeared to be safe and effective for treatment of systemic candidal infection in the neonate.

Pursley et al. (35) describe three infants born to women who were receiving fluconazole through or beyond the first trimester of pregnancy. All of the infants had congenital anomalies; no other drug was implicated. Only one of the three infants survived. Their anomalies, similar to those observed in animal studies, were largely craniofacial, skeletal (i.e., thin, wavy ribs and ossification defects), and cardiac. One of these infants was previously reported as having Antley-Bixler syndrome; however, given the chronology described herein and the similarity of this infant to the others, Pursley et al. conclude that her deformities also represent the potent teratogenic effect of fluconazole.

The prevalence of malformation was 3.3% (four cases) among the 121 women, who

had used fluconazole in the first trimester, and 5.2 % (697 cases) in offspring to controls (odds ratio:0.65, 95% confidence limits 0.24-1.77). Furthermore, Sorensen et al. (36) did not find any significant elevated risk of preterm delivery (odds ratio:1.19, 95% confidence limits:0.37-379). These authors showed no increased risk of congenital malformations, low birth weight or preterm birth in offspring to women who had used single dose fluconazole before conception or during pregnancy. The majority of fluconazole-exposed pregnancies were in women who received common therapeutic doses of 150 mg (56% of pregnancy) or 300 mg (31%). Oral fluconazole exposure was not associated with an increased risk of birth defects overall (210 birth defects among 7,352 fluconazole-exposed pregnancies, [prevalence 2.60%] and 25,159 birth defects among 968,236 unexposed pregnancies [prevalence, 2.60%]; adjusted prevalence odds ratio, 1.06; 95% confidence interval 0.92-1.21). In addition oral fluconazole exposure was not associated with a significant increased risk of 14 of 15 types of birth defects previously linked to azole antifungal agents: craniosynostosis, other craniofacial defects, middle-ear defects, cleft palate , cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary-artery hypoplasia, ventricular septal defects, and hypoplastic left heart. A significantly increased risk of tetralogy of Fallot was observed (7 cases in fluconazole-exposed pregnancies [prevalence, 0.03]; adjusted prevalence odds ratio, 3.16; 95 confidence interval, 1.49- 6.71). Oral fluconazole was not associated with a significant increased risk of birth defects overall or of 14 of the 15 specific birth defects of previous concern. Fluconazole exposure may confer an increased risk of teratology of Fallot (37).

Among 1079 women who filled a fluconazole prescription during the first trimester, 797 (74%) received a total of 150 mg of fluconazole, 235 (22%) received 300 mg of fluconazole, 24 (2%) received 350 mg of fluconazole and 23 (2%) received 600 mg of fluconazole. These women gave birth to 44 (4.1%) infants with congenital malformations. The 170 453 women without fluconazole prescription gave birth to 6152 (3.6%) infants with congenital malformations. For congenital malformation overall, the adjusted prevalence odds ratio associated with the first-trimester fluconazole use was 1.0 (95% confidence interval: 0.8-1.4). Norgaard et al. (38) found no overall increased risk of congenital malformations after exposure to short-course treatment with fluconazole in early pregnancy.

Fluconazole is reported to act as a teratogen when used continuously at a dosage of 400-800 mg daily. Lopez-Rangel and Van Allen (12) report the case of a 9-month-old male born to a 30-year-old woman following a 37-week pregnancy. The pregnancy was complicated by maternal human immunodeficiency virus (HIV) infection and multiple drug exposure, including fluconazole (400 mg/day) until the fifth month and then from 6 months to term, efavirenz, nevirapine, methadone, dapsone, pentamidine, and trimethoprim-sulfamethoxazole. At birth the infant had seizures related to neonatal abstinence syndrome and was noted to have multiple congenital anomalies. On examination at age 9 months, he had craniosynostosis secondary to coronal and lambdoidal suture closures, shallow orbital region, hypoplastic supraorbital ridges, hypertelorism, and mild ptosis. He had radioulnar synostosis and metacarpophalangeal-proximal interphalangeal symphalangism of D2-D5 bilaterally. The findings of cranial synostosis, multiple symphalangism, and

long-bone abnormalities in this case are typical of other reported cases of fluconazole embryopathy. This patient showed no evidence of embryopathy due to efavirenz, and he did not have the features of Antley-Bixler or other craniosynostosis syndromes. Prenatal exposure to fluconazole provides additional evidence that prenatal fluconazole exposure has a clearly identifiable phenotype.

3-2. Pharmacokinetics of fluconazole in neonates

The kinetic parameters for all the studies referenced here are summarized in (Table 1). Krzeska et al. (39) administered fluconazole intravenously at the dosage of 3 mg/kg to 14 patients aged from 9 days to 4.4 months. The half-life was shorter in neonates than in adults, the clearance and the distribution volume were greater in neonates than in adults.

Three infants were born at gestational age 24, 28 and 29 weeks. All were mechanically ventilated for 2 weeks (40). All developed Candida albicans (at least two positive blood and urine cultures over 5 days in each patient) and received oral fluconazole. The first patient received oral 5 mg/kg fluconazole for 42 days. The second patient received oral fluconazole at the dosage of 4 mg/kg per day for 21 days. After a microbiologic relapse (two positive blood culture 4 days after treatment) the dosage was increased to 6 mg/kg per day and continued for 20 more days. The treatment for patient 3 was 4.5 mg/kg per day of oral fluconazole for 28 days. At the end of treatment and during follow up, all blood and urine cultures were negative. Pharmacokinetic studies were performed on treatment day 20. Cmax and Cmin were 502$\pm$2.1 and 8.8$\pm$2.7 µg/ml, respectively. The AUC was 175.0$\pm$ 52.2 µg.h/ml.

Nahata et al. (41) administered fluconazole a single orally or intravenously dosage of fluconazole at the dosage of 6 mg/kg/day to 6 infants with a gestational age of 30.1$\pm$5.5 weeks (range, 26 to 40 weeks) and the postnatal age was 1.71$\pm$0.76 months (range, 0.75 to 2.7 months). The Cmax, AUC and, the apparent clearance were 10.08$\pm$2.75 µg/ml, 440.6$\pm$13.7 µg.h/ml and 0.23$\pm$0.05 ml/min/mg, respectively. These authors did not report the half-life and the distribution volume of fluconazole. Piper et al. (16) administered intravenously a loading dose of 25 mg/kg fluconazole followed by a maintenance dose of 12 mg/kg every 24 hours for 4 additional days to 8 infants <60 days old. Median gestational age at birth was 37 weeks, median postnatal was 16 days and the median birth weight was 2,800 grams. Infants were receiving mechanical ventilation at the time of the study drug medication administration; one infant was receiving extracorporeal membrane oxygenation. The median AUC was 479µg.h/ml (range 347-496 µg.h/ml). Infants were given an intravenous loading dose of 25 mg/kg followed by maintenance therapy of 12 mg/kg. infants receiving 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 therapy for confirmed invasive candidiasis at discretion of the primary medical team. A loading dose of fluconazole (25 mg/kg) was safe in this small cohort of young infants and achieved the therapeutic target more rapidly than traditional dosing of 6 mg/kg. There were no subjects with positive blood culture. Two infants had fungal urinary tract infections (Candida tropicalis and yeast not further specified).

Chryseobacterium was isolated from lung tissue in one infant. In this small cohort of infants, fluconazole clearance was highly variable with a range of 0.53 to 1.62 ml/min/kg. After the administration of a single intravenous loading of fluconazole, 5 of 8 infants (53%) achieved the therapeutic target $AUC_{0\text{-}24}$ >400 µg.h/ml,

and all infants achieved a 24-hours trough concentration >8 µg/ml. After multiple doses, fluconazole accumulation was apparent as evidenced by an increase in median trough concentration at 24, 48 and 96 hours. The lowest fluconazole exposures were observed in 2 infants with severe anasarca. The third infant with sub-therapeutic fluconazole exposure was being supported by the extracorporeal membrane oxygenation. The median AUC_{0-24} of the 7 infants, excluding the 1 supported by extracorporeal membrane oxygenation, was 479 µg.h/ml (range, 271- to 499 µg.h/ml). The highest AUC_{0-24} was observed in an infant with an elevated serum creatinine (1.2 mg/dl).

Watt et al. (42) determined the pharmacokinetics of fluconazole in 9 infants with a postnatal age of 19 days (range, 1-113 days) undergoing extracorporeal membrane oxygenation. Infants received either prophylactic fluconazole per study protocol once a week (25 mg/kg administered intravenously). Fluconazole was also administered per standard of care (12 mg/kg administered intravenously daily) if the children had a known or suspected fungal infection. Infants on prophylactic fluconazole continued to receive 25 mg/kg once weekly for the duration of their extracorporeal membrane oxygenation course. Duration of treatment for infants with suspected or culture-proven fungal infection was at the discretion of the treating physician. The AUC_{0-24} was 343$\pm$44 µg.h/ml in the infants that received a single dose of fluconazole and 364$\pm$42 µg.h/ml in the infants who received multiple dose of fluconazole. After the first dose, 7 of 9 infants (78%) achieved the prophylaxis target of T>MIC (4 mg/ml) for > 84 hours, which was 50% of the dosing interval (43). After multiple doses of fluconazole, 5 out of 7 achieved the prophylaxis target, and none achieved the therapeutic target.

Brammer and Coates (1) studied the pharmacokinetics of fluconazole in 12 prematures neonates. Fluconazole (6 mg/kg) was administered intravenously. The distribution volume varied with age, being greatest during the neonatal period (1.18 to 2.25 l/kg) and decreasing by young adulthood to a value similar to that reported for adults (0.7 l/kg). In neonates, fluconazole was eliminated slowly, with a mean elimination half-life of 88.6 at birth, 67.5 hours approximately one week later and 55.2 approximately two weeks after birth. Fluconazole is predominantly eliminated by renal route as unchanged and metabolism accounts for only a minor proportion of fluconazole clearance.

Twelve premature infants with a mean gestational age of 27.4 weeks and a mean birth weight of 912 grams receiving fluconazole prophylactically from the first day of life were enrolled in an open phase I-II pharmacokinetics, safety and tolerance trial (44). Up to 5 doses of 6 mg/kg were administered intravenously every 72 hours during the first 2 weeks of life. The first dose was given 8.6 to 35.7 hours (mean, 23.7 hours) after birth. Pharmacokinetic characteristic of fluconazole were determined after the first, third, and fifth doses. The mean peak and trough concentrations after 3 doses were 5.5 and 2.6 µg/ml, 12.8 and 4.3 µg/ml, and 10.0 and 2.9 µg/ml (P=0.0002 and 0.07), respectively. The clearance increased with increasing postnatal age, whether it was corrected for weight (r=0.61; P=0.007). Similar correlation was not found between postnatal age and half-life. No simple correlations was evident between total clearance of fluconazole and serum creatinine (clearance/kg, r=0.02, p=0.9; clearance, r=0.06, P=0.8). In multiple regression analysis, gestational age, postnatal age, weight and serum creatinine could explain only 27.5% (r=0.53; P=0.055). The variance in distribution volume was explained to 49.2% (r=0.70,

P=0.012) by gestational age, weight, and log of postnatal age. There was a significant correlation of distribution volume with body weight (r=0.60; P=0.003). The kinetic parameters in adults are reported by Thummel et al. (13).

Table 1: Pharmacokinetic parameters of fluconazole in neonates

Number of cases	Dose (mg/kg/day)	Development stage	Half-life (hours)	Clearance (ml/min/kg)	Distribution volume (l/kg)	Reference
14	3 IV	9 days-4.4 months	25.5±2.2	0.63±0.06	1.17±0.08	39
3	4 to 6 Oral or IV	Preterm	34.7±9.3	0.42±.05	1.4±0.4	40
8	Note A	Term	54.4±29.7	0.27±0.10	1.1±0.3	16
9	25 mg/kg once a week IV	Preterm and term	62.0±28.7	0.34±0.19	1.50±0.21	42
7	12* IV		75.7±58.1	0.36±16	1.80±0.37	
12	6 IV	Preterm 1 day old	88.6	NA	1.18	1
		Preterm 1 week old	67.5	NA	1.84	
		Preterm 2 weeks old	55.2	NA	2.25	
7	6 every 72 hours IV	Preterm, first dose **	88.6	0.18	1.18	44
9		Preterm, third dose**	67.5	0.33	1.84	
4		Preterm, fifth dose**	55.2	0.52	2.5	
---	---	---	32±5	0.27±0.07	0.60±0.11	13

NA =not available; IV=Intravenous; Note A=Subjects were given an intravenous loading dose of 25 mg/kg followed by a maintenance therapy of 12 mg/kg/day; *Multiple doses; ** The first dose was given 8.6 to 35.7 hours (mean 23.7 hours) after birth; The subsequent dosing interval was chosen as 72 hours.(Figures are the mean or the mean± SD).

4-DISCUSSION

About 3% to 4% of the very-preterm infants developed candidiasis (2, 3) and about 30% of these infants died (9). Fluconazole is increasingly used in the treatment of invasive Candida albicans infection. Oral fluconazole is widely used to treat topical infection in adults and is now starting to be used for this purpose in infants. There are several studies showing that in preterm infants with invasive Candida infection fluconazole controlled candidiasis in a higher frequency than in control infants (no treated) (18, 21-32). The dose of fluconazole used by different authors varies in different studies. To reach the fluconazole exposure target AUC_{0-24} of ≥400 µg.h/ml in critically ill infants, the recommended dosage of fluconazole is 12 mg/kg/day. Fluconazole is a safe and effective drug against Candida infection. Twice weekly prophylactic dosing of fluconazole prevents invasive candidiasis without promoting resistance to Candida species in high-risk preterm infants. Kicklighter et al. (27) and Brammer and Coates (1) administered intravenously fluconazole at the dose of 6 mg/kg daily. Saxen et al. (44) administered intravenously 6 mg/kg of fluconazole every 72 hours. Krezeska et al. (39) administered fluconazole intravenously 3 mg/kg daily. Wenzl et al.

(40) administered fluconazole at a daily dosage of 4 to 6 mg/kg orally or intravenously. Piper et al. (16) gave an intravenous loading dose of 25 mg/kg followed by a maintenance therapy of 12 mg/kg/day. Watt et al. (42) administered an intravenous dose of fluconazole of 25 mg/kg weekly or 12 mg/kg fluconazole daily. All these doses controlled candidiasis. Watt et al. (42) state that fluconazole has a long half life and a loading dose of 25 mg/kg is useful to reach the steady state of fluconazole quickly.

Maede et al. (19) compared the efficacy of fluconazole and micafungin in the control of candidiasis in extremely preterm infants. The prophylaxis was successful in 39% of the fluconazole group and 71% in the micafungin group. Micafungin was superior to fluconazole as prophylaxis against fungal infection in extremely preterm infants. Fluconazole is associated with cholestasis in extremely preterm infants. Bhat et al. (21) observed that a dosing of fluconazole every 72 hours for up to 6 weeks has less severe cholestasis than more frequent treatment of fluconazole.

Oral nystatin prophylaxis is effective, is not toxic, and is not associated with cholestasis and should be used in preterm infants. The sensitivity of the fungal isolates to fluconazole therapy did not change during the study, and no adverse effects of the fluconazole therapy were documented. Prophylactic administration of fluconazole during the first six weeks of life is effective in preventing fungal colonization and invasive fungal infection in preterm infants. Fluconazole is effective in controlling Candida albicans, Candida tropicalis, Candida guillermondii, and Candida krusei. Fluconazole was effective in 82.3% of these cases without side effects (29).

All of the infants born to mothers who received 400 to 800 mg fluconazole through or beyond the first trimester of pregnancy had congenital anomalies (12). A single dose of 150 or 300 mg early in pregnancy does not increase the risk of birth defects. The half-life of fluconazole ranges in a high interval and in several cases is longer than in adults. The half-life of fluconazole decreases with neonatal maturation. In preterm infants 1 day old, 1 week old, and 2 weeks old the half-life of fluconazole is 88.6, 67.5 and 55.2 hours, respectively. In adults, the half-life of fluconazole is 32 hours (13). Saxen et al. (44) administered fluconazole intravenously at the dosage of 6 mg/kg. The first dose was given 8.6 to 35.7 hours (mean 23.7 hours) after birth. The subsequent dosing interval was chosen as 72 hours. The half-life of fluconazole was 88.6, 67.5 and 55.2 hours on the first, second and third dose, respectively. The clearance of fluconazole increases with neonatal maturation. It is 0.18, 0.33 and 0.52 ml/min/kg at the first, second and third dose, respectively (44). In neonates, the clearance of fluconazole ranges from 0.18 to 0.63 ml/min/kg, and in adults is 0.27 hours (13). Fluconazole is mainly eliminated by the renal route (1) and the renal elimination rate of fluconazole increases with renal maturation. This explains the shorter fluconazole half-life and the greater clearance of this drug with the neonatal maturation.

The distribution volume ranges in a small interval in neonates, it ranges from 1.1 to 2.5 l/kg. In adults it is 0.60 l/kg (13). The larger distribution volume in neonates than in adults indicates that the accumulation of fluconazole is larger in neonates. In conclusion, fluconazole is an active and safe drug for standard neonatal systemic antifungal therapy. About 3% to 4% of very-preterm infants developed candidiasis and 30% of these infants died. The dose of fluconazole differs in various studies and ranges from 3 to 12 mg/kg. All these doses have antifungal activity. A loading dose of 25 mg/kg is useful to reach the steady-state

of fluconazole quickly. Micafungin is superior to fluconazole as prophylaxis against fungal infection in preterm infants. Oral nystatin is effective and nontoxic and is not associated with cholestasis. A dosing of fluconazole every 72 hours for up to 6 weeks has less severe cholestasis than more frequent treatment of fluconazole. A dosage of 400 to 800 mg daily during the first trimester of pregnancy acts as a teratogen. A single dose of fluconazole of 150 or 300 mg in the first trimester of pregnancy does not yield neonatal abnormalities. The half-life of fluconazole decreases in the first 3 weeks of life and in this period of time the clearance of fluconazole increases. Fluconazole is mainly eliminated by the renal route and the renal elimination rate increases with the neonatal maturation.

5- CONCLUSION

Fluconazole is a type of medicine called an antifungal. It is used to treat or prevent infections caused by certain types of yeast or fungus. Fluconazole is a synthetic antifungal agent that can be used for the treatment of Candida albicans and other fungal infections. Infants with invasive candidiasis required a minimum of 12 mg/kg/day of fluconazole to achieve therapeutic exposure, an AUC of 400 mg*hr/L to meet the PK/PD index of AUC/MIC ≥50 for Candida isolates at the susceptibility breakpoint, MIC 8µg/ml. For the early prevention of candidiasis, dosages of 3 or 6 mg/kg twice weekly have demonstrated efficacy in randomized controlled trials and can maintain the fluconazole concentrations above 2 or 4 µg/ml, respectively, for >40% of the dosing interval. For the late prevention of candidiasis, dosages of 6 mg/kg, every 48 to 72 hours based upon gestational age at birth and postnatal age, are reasonable based upon adult exposures achieved after 100 mg/day dose and the ability to maintain fluconazole concentration above an MIC of 4 for at least 40% of the dosing interval. Late prevention strategies have not been subjected to randomized controlled trials. These results are based on simulated clinical trials. Confirmatory, prospective trials of fluconazole exposure, safety, and efficacy are needed.

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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