

FLUCONAZOLE IN THE MANAGEMENT OF NEONATAL SYSTEMIC CANDIDIASIS

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Objective: To evaluate the role of Fluconazole in the management of neonatal systemic candidiasis. **Design:** Descriptive, retrospective analysis. **Subjects:** 23 neonates diagnosed as systemic candidiasis based on clinical suspicion with blood and/or urine culture positive for *Candida* were treated with Fluconazole (5 mg/kg/day) for >7 days. **Results:** Babies had mean birth weight 1590+533 g, mean gestation 32.3+3.1 wks and fungal sepsis was diagnosed at a mean age of 14.3+7.9 days. *Candida albicans* (43.5%), *C. tropicalis* (21.7%), *C. guilliermondii* (13%), *C. parapsilosis* (13%) and *C. krusei* (8.7%) were the species isolated. Fluconazole was effective in 82.3% cases with no side effects. Four resistant cases were *C. parapsilosis* (n=2), *C. albicans* (n=1) and *C. guilliermondii* (n=1) and there were three deaths, all in resistant cases though one death was unrelated to candidemia. **Conclusion:** Fluconazole is a safe and effective drug for neonatal systemic candidiasis.

Key words: Neonate, *Candida*, Fluconazole.

FUNGAL infections are rarely considered in neonates with signs of sepsis because bacteria and virus are more common causes of acute neonatal illness(1). With improving survival of high risk newborns by modern day technology, incidence of systemic fungal infection has been increasing(2, 3). Low birth weight, prolonged indwelling catheters, broad spectrum antibiotics, mechanical ventilation, parenteral nutrition, have all been identified as risk factors for disseminated candidiasis(1-3).

Amphotericin B, the gold standard for systemic antifungal therapy has several drawbacks like intravenous administration, renal toxicity and poor CSF penetration. Flucytosine has limited spectrum of activity with multiple toxic effects. Ketoconazole

and itraconazole penetrate poorly into CSF and the former is potentially hepatotoxic and inhibits testosterone and adrenal steroids synthesis. Administration of fluconazole, a new triazole derivative can be a good alternative in view of its good CSF penetration, concentration in urine and minimal adverse reaction(4). The present retrospective study was undertaken to evaluate the efficacy of fluconazole in treating neonatal systemic candidiasis.

Subjects and Methods

A retrospective analysis was carried out on neonates who received fluconazole for 7 days or more as the first line drug against systemic candidiasis between September 1994 to August 1995. The criteria for diagnosis of systemic candidiasis were clinical

suspicion (*i.e.*, persistent lethargy, not gaining weight, apnea, persistent or recurrent pneumonia, feed intolerance) and positive candidal blood and/or urine culture. Fluconazole was used in the daily dose of 5 mg/kg/day for 3-4 weeks. It was administered intravenously in all cases initially and changed to oral, once enteral feeding was started. For intravenous administration, 100 ml bottle containing 2 mg/ml of fluconazole was used while for oral administration, 50 mg capsules were used and dose prepared by pharmacist.

Fluconazole was considered effective based on clinical improvement with sterile blood/urine culture on completion of therapy. Failure of therapy was defined by lack of clinical response/deterioration (other causes ruled out) by 7th day of fluconazole treatment and blood/urine continuing to yield *Candida* at or beyond 7 days of fluconazole administration. Fluconazole was replaced by Amphotericin B in fluconazole resistant cases.

Results

A total of 23 neonates received fluconazole for systemic candidiasis during this period. The mean gestation of these cases was 32.3 ± 3.1 wks while mean birth weight was 1590 ± 533 g. Fungal sepsis was diagnosed at a mean age of 14.3 ± 7.9 days. Three neonates had already acquired systemic candidiasis by day 7 of life (13%).

Clinical findings on which systemic candidiasis was suspected in these cases were: persistent pneumonia (56.5%), lethargy (43.5%), not gaining weights (30.4%), apnea (17.4%), recurrent pneumonia (8.7%) and feed intolerance (8.7%). They had the following predisposing factors for candidiasis: prematurity (87%), broad spectrum antibiotics usage (100%), IV fluids (100%), ventilation (56.5%), exchange transfusion (56.5%) and parenteral nutrition (13%). Blood culture was positive for *Candida* in 87% cases, urine culture

in 26.1%, both blood and urine in 21.7% and CSF in 4.3% cases. The *Candida* species isolated from blood/urine were: *C. albicans* (43.5%), *C. tropicalis* (21.7%), *C. guilliermondii* (13%), *C. parapsilosis* (13%) and *C. krusei* (8.7%).

Fluconazole was therapeutically effective in 82.3% cases. Only 4 out of 23 cases were clinically resistant to fluconazole. These 4 resistant cases were *C. parapsilosis* (n=2), *C. Guilliermondii* (n=1) and *C. albicans* (n=1). Three babies (13%) died at a mean age of 40 days and all of them were resistant to fluconazole. The cause of death in one case (*C. guilliermondii*) was unrelated to candidemia (died of intestinal obstruction with necrotising enterocolitis), but the other 2 cases died due to persistent fungal pneumonia and apnea (both had grown *C. parapsilosis* in blood).

Discussion

Systemic candidiasis is an increasing problem among high risk neonates due to greater use of invasive treatments like hyperalimentation, prolonged ventilatory support, broad spectrum antibiotics and consequent survival of smaller and sicker infants(2-3). The increase in fungal infections have been accompanied by development of new, less toxic, systemically active alternatives to amphotericin B like fluconazole and itraconazole(4). Unfortunately, the role of fluconazole in treating neonatal candidiasis has been documented only in a few case reports in literature(5-9). Fluconazole has proved effective against disseminated candidiasis, candidal renal bezoars, osteomyelitis, brain abscess and meningitis.

Fluconazole has several advantages over other antifungal agents. It is well absorbed orally (oral absorption of amphotericin B is negligible and ketoconazole is variable), has low affinity for plasma proteins (amphotericin B, ketoconazole and itraconazole are

> 90% bound to plasma proteins), long half life of 22 h (ketoconazole 8 h and itraconazole 17 h), adequate concentration in urine (amphotericin B, ketoconazole and itraconazole are minimally present in urine), excellent CSF penetration (poor penetration of amphotericin B, ketoconazole and itraconazole), highly specific for fungal cytoP450 system compared to other azoles, minimal adverse reactions (highly toxic side effects of amphotericin B and flucytosine), good spectrum of activity and no adverse effect on immune system (unlike itraconazole)(4,5).

The present study has shown clinical efficacy of fluconazole in 82% cases with no adverse side effects. Another study on children found the efficacy of fluconazole to be 88% in systemic candidiasis(10). Most species of *Candida* are susceptible to fluconazole but vary in sensitivity. MIC 90 values are 0.25-6.4 mg/L for *C. albicans* and *C. tropicalis* while for *C. krusei* it is > 50 mg/ L (11). In the present study, both cases of *C. krusei* responded to fluconazole. The highest resistance was reported for *C. parapsilosis* infection (12 mg/kg/day instead of 6 mg/kg/day)(10). The increased mortality with *C. parapsilosis* as found by this study is not corroborated by (12) another series which found mortality to be higher in infection with *C. albicans* than *C. parapsilosis*. This may be due to the use of amphotericin B with flucytosine in that series as against fluconazole in the present study. *C. albicans* is inherently more susceptible to fluconazole than other candidal species(11).

In conclusion, fluconazole is an effective and safe drug against systemic neonatal candidiasis. Its good efficacy against *C. krusei* and higher resistance against *C. parapsilosis*, warrants further studies on the efficacy of fluconazole against these

candidal species. Also controlled studies should be conducted to evaluate the comparative efficacy of fluconazole and amphotericin B in neonates with systemic candidiasis.

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