

A Case Presentation of Voriconazole Therapy in a Brochopulmonary Dysplasia

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ABSTRACT

Premature infants may be more vulnerable to fungal infections because of their immature immune system, poorly developed epithelial skin and mucosal barriers, and the high rate of invasive procedures, such as central venous catheters and intubation, which compromise host defenses (e.g. skin integrity). Voriconazole is a newer systemic antifungal agent effective against *Candida* and *Aspergillus*. There are few reports of its safe use in newborns. We report the first case report - a 29 gestational age-900 gram baby girl of safe Voriconazole use in a critically ill with profound pancytopenia -huge hepatosplenomegaly due to fungal infection resistant to amphotericin B. with beginning oral Voriconazole all liver functions tests what were severely abnormal returned normal with normalizing of the size of liver and spleen. It was noted to be safe and well tolerated by the newborn. Because of oral administration of it, voriconazole is a very good choice for fungal infections in neonates.

Keywords: Antifungal, Brochopulmonary dysplasia, Newborn, Voriconazole

Introduction

Systemic fungal infection occurs in up to 4% of very low birth weight infants the incidence of *Candida* and noncandidal fungal infections in neonates appears to be increasing, particularly in premature infants (1). Premature infants may be more vulnerable to fungal infections because of their immature immune system, poorly developed epithelial skin and mucosal barriers, and the high rate of invasive procedures, such as central venous catheters and intubation, which compromise host defenses (e.g. skin integrity). Parenteral nutrition and prolonged courses of broad spectrum antibiotics empirical therapy pending therapy is advised in this situation (2). One of the antifungal drugs of choice is Voriconazole. There are few reports of its use in newborn for the first time it was used in critically ill neonates with cardiac and respiratory failure, without any significant side effect (3, 4). Therefore the largest clinical studies of Voriconazole in the pediatric and newborn patients are needed. Being safe with its oral route it is a very good choice of antifungal therapy in neonates especially in very low birth weight that are very responsible to fungal infections.

Case presentation

A 29 gestational age-900 gram baby girl was born with severe respiratory distress. She received nasal CPAP. CMV -DNA-PCR was negative at the first two week, but after about one month it was positive and because of huge hepatosplenomegaly and pancytopenia with she received Gancyclovir. Her urine CMV -DNA PCR turned to negative, after getting parenteral nutrition, Her blood and suprapubic urine culture were positive with *Candida nonalbicans*. the CSF was negative. A trial of amphotericin B was begun. A week later there wasn't any improvement in general condition with positive blood and urine culture so antifungal therapy changed to oral Voriconazole (4mg/kg/dose twice a day). after about three days all cultures turned to negative and about one week was very good. After 3 weeks she was very good in condition & weight gain but oxygen dependent due to about three months due to her brochopulmonary dysplasia.

Discussion

Because untreated *Candida* infections, especially in infants with VLBW, are associated with considerable morbidity and mortality, on the other hand with very long intravenous therapy with amphotericin ,long hospital stay ,the cost benefit of an oral kind ,effective with low side effects is very important (2,4). In this case with a very serious systemic non albicans candidiasis we tried

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Voriconazole 4mg per kilogram twice daily for about 4 weeks in a very preterm neonate with huge hepatosplenomegaly due to non albicans candidiasis sepsis. Our patient, fungal sepsis was completely cured, with very good tolerance and response. We checked liver functions-renal -functions CBC -QT interval -ophthalmologic consult twice a week. Voriconazole is a triazole derived from fluconazole clinically effective as a systemic antifungal against *Candida*, *Aspergillus* and unusual organisms *Fusarium* and *Pseudallescheria* (5). The Voriconazole package insert warns about QT interval prolongation/ventricular tachycardia/torsade de pointes on the basis of a few previous cases. In the literature, 3 cases of QTC interval prolongation have been reported. Risk factors for QT interval prolongation are well documented: female, electrolyte imbalance, drug interactions, intravenous route of administration, inherited long QT interval, excessive dosing of proarrhythmogenic drugs, and heart disease. Electrocardiograms should be performed in patients at risk of cardiac complications when Voriconazole is administered. Nine cases of acute renal failure were reported; in 2 of these, intravenous Voriconazole was administered. In clinical trials, acute renal failure was observed in 3.9% of patients, and populations exposed to Voriconazole may be more susceptible to abnormalities in renal function due to their underlying conditions (Neutropenic, bone marrow transplantation, sepsis). In patients with impaired renal function, intravenous Voriconazole can lead to accumulation of the vehicle sulfobutyl ether beta cyclodextrin sodium, with resultant renal failure⁶. The other adverse effects of Voriconazole include fever, gastrointestinal symptoms, headache, hypotension, visual disturbances, Stevens Johnson syndrome, toxic epidermal necrolysis, pancreatitis, hepatitis, and jaundice. Visual disturbances have been reported in 45% of patients after using Voriconazole in clinical trials. The most commonly reported adverse events included elevation of hepatic transaminases or bilirubin (n=8), skin rash (n=8), abnormal vision, and photosensitivity reaction Liver function should be monitored before treatment, and then at a 2- to 4-week intervals. In our case, we did not observe any serious complications caused by Voriconazole⁶. The cost of antifungal therapy has remained a major factor in its use especially when liposomal therapy is used. The other major advantage of Voriconazole is the cost which is about 12% of the cost of liposomal amphotericin for a 2 week course of antifungal therapy (4). All azoles work by inhibiting cytochrome p 450 dependent enzymes, which result

in compromise of the cell membrane integrity. Other drugs working via the cytochrome p 450 include phenytoin, quinidine and warfarin, which may interact with Voriconazole. But critically ill cardiac newborn may potentially be on several drugs, which could interfere with Voriconazole. The commonly used drugs which interfere with Voriconazole include barbiturates, rifampicin, cisapride, midazolam, sildenafil, tacrolimus and omeprazole (7). The cases discussed above were on several medications including anti-arrhythmic, inotropic, several groups of antibiotics, and prokinetic agent and diuretics baby during the period of use. During the period of administration we checked liver function tests -QT intervals -CBC in spite of hepatosplenomegaly-hepatic liver dysfunction we use it after about 5 days all liver function tests were normal ,with normalization of size of liver and spleen the drug In conclusion, we consider that Voriconazole can be administered safely to neonates Although we cannot recommend the use of Voriconazole in pediatric patients based on the single case, our experience with this patient suggests that Voriconazole may be considered in a neonate with fungal hepatitis. Further research is needed to fully assess the clinical potential of Voriconazole for neonatal safety (3).

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References

1. McDonnell M. Fungal infections in the newborn. *Seminars in Neonatology*. 1996; 1(2):141-145.
2. Benjamin DK, Stoll B, Walsh M, Sanchez P., Das A, et al. Neonatal candidiasis :Epidemiology, Risk Factor, and Clinical Judgment. *Pediatrics*. 2010;126(4):e865-e875.
3. Das S, Shivaprakash MR, Chakrabarti A. New antifungal agents in pediatric practice. *Indian Pediatrics*. 2009;46(3):225-231.
4. Kohli V, Taneja V, Sachdev P, Joshi R. Voriconazole in Newborns. *Indian J Pediatrics*. 2008; 45(3):236-238
5. Abuhammour W, Habte-Gaber E. Newer antifungal agents. *Indian J Pediatrics*. 2004;71(3):253-259.
6. Eiden C, Peyriere H, Cociglio M, Djezzar S, Hansel S, Blayac JP, et al. Adverse effects of Voriconazole :analysis of the French Pharmacovigilance Database. *Ann Pharmacother*. 2007;41(5):755-763.
7. Venkataramanan R, Zang S, Gayowski T, Singh N. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob Agents Chemother*. 2002; 46(9): 3091-3093.