Voriconazole in Newborns

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ABSTRACT

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 series of safe Voriconazole use in critically ill newborns with cardiac disease along with several other cardiac drugs without any significant drug interaction or side-effect.

Key words: *Antifungal, Heart disease, Newborn, Voriconazole.*

INTRODUCTION

Critically ill newborns are predisposed to systemic fungal infections. The available antifungals for systemic infections are intravenously administered. Voriconazole is an oral and systemically effective antifungal agent(1-3). We report our experience with use of Voriconazole in sick newborns with cardiac disease.

CASE REPORTS

***Case* I:** A 29-day-baby was admitted with slow ventricular tachycardia which was present for several days and had resulted in tachycardia-induced-cardio-myopathy. Echocardiogram revealed a structurally normal heart, depressed LV function with an ejection fraction of 10%. Myocarditis was ruled out by normal troponin I levels. A trial of digoxin and later beta-blockers failed to control the arrhythmia; finally intravenous amiodarone was effective but induced a heart block. Transvenous temporary pacing and ventilatory support were required. Hospital acquired infection in form of *Klebsiella* spp. was noted and treated with Meropenem for a total of 14 days. A later blood culture grew *Candida pelliculosa* for which intravenous liposomal amphotericin B was added. A negative fungal culture was noted a week later. Since the child's cardiac condition was stable by the time 10 days of IV amphotericin B was completed, the antifungal treatment was changed over to oral voriconazole (4 mg/kg/dose twice a day) in anticipation of discharge. The baby was also receiving amiodarone, propranolol, frusemide, and cefepime, simultaneously. Voriconazole was administered for a total of 2 weeks and no side-effects or drug interactions were noted.

***Case* II:** A term AGA baby was referred to our hospital on day 4 of life with severe respiratory distress, absent pulses and poor perfusion. Echocardiography confirmed type II aortopulmonary (AP) window with type A interrupted aortic arch (IAA). The baby was taken up for repair of IAA and closure of AP window on day 3 of admission. Postoperatively baby developed a systemic infection with *Burkholderia cepacia*. This was initially treated with meropenem and co-trimoxazole. Budding yeast cells (*Candida* spp.) were isolated from the endotracheal aspirates for which liposomal amphotericin B was also administered. On post-operative day (POD) 10, due to dangerously low and persistent thrombocytopenia, amphotericin B was replaced by oral voriconazole (4 mg/kg/dose twice a day), which was given for a total of 3 weeks. Baby was simultaneously also receiving dopamine, dobutamine, milrinone, antiobiotics and frusemide. On POD 64 blood culture was again positive for *Candida* and baby was started on amphotericin B

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and given for a total of 2 weeks (culture negative after 1 week). The baby was discharged on oral voriconazole, which was continued for another 2 weeks. No drug interactions were noted.

DISCUSSION

Voriconazole is a triazole clinically effective as a systemic antifungal against Candida, Aspergillosus and unusual organisms *Fusarium* and *Pseudallescheria boydii*(4). Both the index patients were documented to have *Candida* spp. infection on 3 different occasions. Indication of use of voriconazole was ease of use of reliable antifungal agent orally in critically ill cardiac patients with prolonged hospitalization and multiple interventions (central lines, tranvenous pacing, cardiac surgery). On one occasion voriconazole was used due to persistent thrombocytopenia which was partly at least contributed to by amphotericin B.

The spectrum of activity of voriconazole gives it an inherent advantage over other antifungals. Voriconazole is active against all *Candida* species (including resistant strains). It has up to 60-fold lower minimum inhibitory concentration for *Candida* species. It is active against even those strains of *Candida krusei* and *Candida glabrata* that have been found to be fluconazole resistant, and strains of *Candida albicans* which demonstrate acquired resistance to fluconazole.

One of our concerns was drug interactions in view of the several other drugs administered simultaneously. 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, tacroli-mus and omeprazole(7). The cases discussed above were on several medications including anti-arrhythmics, inotropes, several groups of antibiotics, prokinetic agent and diuretics. The mechanisms of action of these are varied and potential of interactions were checked prior to use. Apart from the interactions, the drug itself was noted to be safe and well tolerated by the newborn babies during the period of use.

The recommended dosage of voriconazole of 4 mg/kg/dose in newborns is much higher than that used in adults as elimination of voriconazole in newborns and children follows the linear kinetics thus requirement of a higher dosage. The recommended duration of therapy is on an average 2 to 3 weeks but has to be individualized to the patient and the type of fungal species grown(1). It must be mentioned that there are no phase III clinical trials in pediatric age group to justify this dosage(1). The safety of IV voriconazole though had been established in immunocompromised children with a dose of 4 mg/kg(8). Voriconazole has been reportedly used in newborns previously. In a report of fluconazole resistant Candida infection in a preterm, intravenous Voriconazole was used along with liposomal Amphotericin B in a preterm baby without side effects or complications(2).

The cost of medical treatment and hospital stay both increase when IV antifungal treatment is given. We have used IV therapy till the patient had to be in the hospital for other reasons and then completed antifungal course with oral voriconazole therapy. This has brought the hospital costs down without compromising on the spectrum of antifungal coverage for systemic infection. In a direct comparison of amphotericin with intravenous voriconazole for empiric fungal infection, Walsh, *et al.*(9) noted voriconazole to be superior with fewer side effects.

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.

In conclusion, voriconazole appears to be a safe oral antifungal to be used in critically ill cardiac newborns. Advantages include oral route of administration with wide spectrum of coverage without the renal and platelet lowering side effects. In addition, there is a significant cost advantage over liposomal amphotericin.

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Topiramate Associated Hypohidrosis and Hyperthermia

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ABSTRACT

Topiramate is a new antiepileptic drug, used for treatment of partial onset seizure and refractory seizures. Although it is well tolerated in children, some adverse effects including hypohidrosis and hyperthermia are reported. We present two children with epilepsy who were treated with topiramate and developed hypohidrosis and hyperthermia.

Key words: *Adverse event, Epilepsy, Hyperthermia, Hypohidrosis, Topiramate.*

INTRODUCTION

Topiramate is a new antiepileptic drug, effectively used for partial onset seizures, infantile spasms, and refractory absence(1). Chemically it is a sulfamate-substituted monosaccharide and structurally resembles carbonic anhydrase inhibitors with a weak inhibitory effect in vitro. Topiramate has different mechanisms of action: (*i*) blockade of voltage-dependent sodium channel in the neuronal membrane, (*ii*) blockade of kainate type of glutamate receptor, (*iii*) enhanced γ aminobutyric

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