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Compassionate use of voriconazole in newborn infants diagnosed with severe invasive fungal sepsis

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Abstract. – BACKGROUND: Invasive fungal sepsis has become the third most common cause of late-onset infections in many neonatal intensive care units (NICU). The prevalence rate ranges from 2.6% to 16.7% among very-low-birth-weight infants and from 5.5% to 20% among extremely low-birth-weight infants. Despite the development of several new antifungal agents in the past few years, the management of serious fungal infections in the newborn continues to be problematic.

MATERIALS, METHODS AND RESULTS: Voriconazole treatment was given to 17 newborns with invasive fungal sepsis, in initial doses of 2-3 mg/kg twice daily. In spite of the complications of cholestasis and liver function abnormality in 2, the dose regimen was 4-6 mg/kg (loading dose), followed by initial doses of 2-3 mg/kg twice daily. Drug cessation did not occur, and no permanent side effects were observed. In the end, 12 patients had been cured with antifungal treatment.

CONCLUSIONS: Voriconazole at this dosage common with other antifungal agents or alone appears to be a safe and effective antifungal agent for neonatal invasive fungal sepsis. Based on relevant literature, to the best of our knowledge, ours is the largest case series to underline this issue. However, further studies are required to determine the pharmacokinetics (e.g. serum half-life, concentration, time of peak concentration, and distribution) of voriconazole use in newborns.

Key Words:
Newborn, Invasive fungal sepsis, Voriconazole.

Introduction

Invasive fungal sepsis (FS)[1] is currently the third most common cause of late-onset infections in neonatal intensive care units (NICU). Susceptibility is particularly high in premature neonates. The range of prevalence rate has risen from 2.6%-16.7% to 5.5-20% among very-low-birth-weight and extremely low-birth-weight infants, respectively, with an approximate crude mortality rate of 30%[2-4]. Short term complications include persistent infection and significant focal sequelae (e.g., renal fungal bezoars, endocarditis, and meningitis); neonatal invasive FS has also been associated with long-term neurodevelopmental disability[2-4]. *Candida albicans* is the most commonly isolated pathogen in neonatal invasive FS, although *C. parapsilosis*, *C. glabrata*, and *C. lusitaniae* cause clinically similar infections[5-6]. The patterns of transmission are vertical (during delivery from the mother) and horizontal (a hospital-acquired infection from a central catheter).

Currently, four classes of antifungals are used to treat invasive FS,: the polyene macrolides comprising amphotericin B, nystatin, candicindin, natamycin, and mepartricin; a class divided into two groups – the azoles (an older group known as imidazoles) comprising miconazole, ketoconazole, clotrimazole, and econazole, and the triazoles (a newer group) comprising fluconazole, itraconazole, tetraconazole, and voriconazole; the fluorinated pyrimidines including flucytosine; and the echinocandins including caspafungin. Although several new antifungal agents have been developed in the past few years, the management of serious fungal infections in the newborn continues to be problematic. Pharmacological treatment of invasive FS in neonates has traditionally been limited to amphotericin B, flucytosine, and fluconazole. However, the development of newer generation of azoles, such as voriconazole and echinocandins may ultimately expand the therapeutic options for single-agent and combination therapy for resistant or recurrent neonatal invasive FS.

This study presents the results of the use of voriconazole in order to save the lives of in 17 out of 107 newborns under follow-up treatment for the diagnosis of invasive FS, in whom the infection persisted despite conventional therapy.

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Patients and Methods

Study Design and Patient

We performed a retrospective study of newborns followed-up between January 2007 till December 2009 at the neonatal intensive care unit (NICU) of Zekai Tahir Burak Women's Health Education and Research Hospital, the biggest tertiary neonatology unit in Ankara, Turkey. High risk pregnancies were particularly followed-up, and of 25,000 infants born in one year, ~4,000 were followed-up. Of 107 patients who had invasive FS during the study period, amphotericin B treatment was the first-line treatment option, and we used voriconazole in 17 patients with persistent infection in spite of the already administered antifungal therapy in an appropriate dose and treatment duration. Informed consent was taken from parents. Data regarding the demographics, microbiology, risk factors, treatment, acute phase reactant responses and the prognosis were collected from the patients' records. Renal and cranial ultrasonography, echocardiography, eye examination, lumbar puncture, and culture of the cerebrospinal fluid and urine were performed on all patients.

Approval from the local Ethics Committee was obtained.

Diagnosis of Invasive Fungal Sepsis

Diagnosis of invasive FS should be made by isolation of the fungus from the blood of the sick newborn. If *Candida* is not isolated from the blood, demonstration of the fungus in joint fluid, cerebrospinal fluid, urine (by suprapubic aspiration) and other body fluids by direct microscopic examination or culture establishes the diagnosis. Furthermore, serial serum CRP (C-Reactive Protein) and IL-6 values were used for the initial evaluation and follow-up treatment of invasive FS, based on study of Oguz et al[7]. We described the refractoriness to liposomal amphotericin B therapy as CRP positivity due to lack of sensitivity of the blood culture (reported to be < 50%); clinically ill patients had fungal infection with high CRP and low IL-6 levels as shown in our previous studies.

Treatment and Evaluation of Treatment

For the antifungal treatment, Amphotericin B or another drug was chosen according to the antifungal sensitivity test. The response to therapy was evaluated by CRP levels at 72 hours and on the 5. day following commencement of treatment and culture specimens were obtained. According to the initial levels, no decrease or an increase in the CRP level, demonstration of the fungal pathogen in the cultures and "no improvement in the clinical findings", were accepted as "no response". When there was no CRP response despite no culture growth in the culture specimens when under therapy for a week, this was defined as "partial responselessness". In the presence of these life threatening clinical pictures, a change in the treatment mode was planned with the aim of rescuing the patients. The clinician made the decision regarding whether to use the previously administered antifungal in combination with another drug, or for it to be used alone.

A CRP response, culture negativity and clinical improvement were defined as "full recovery". During the treatment, the liver function test results, complete blood count results and newly appearing symptoms were recorded from the file summaries.

Results

Treatment with Amphotericin B, 5 mg/kg/day, 1 hour-infusion as first line treatment was begun in 107 newborns that had been diagnosed with invasive FS. It was found that in 17 (15.8%), the treatment was altered due to no response at all, or partial treatment response. One patient had intracardiac thrombus, four patients had increased renal echogeneity and one patient had increased liver echogenity. No patient had meningitis or characteristics of an abscess of central nervous system.

The means and the standard deviations of the birth weight, gestational age, and the time of diagnosis were 1250 ± 268 g, $29^2 \pm 2^5$ weeks, and 25 ± 14 days, respectively. The median, minimum, and maximum diagnosis times were 24, 8, and 58 days, respectively. The delivery mode was predominantly caesarean section (Table I). Thirteen patients had bacterial sepsis prior to the diagnosis of fungal sepsis. All patients received broad-spectrum antibiotics prior to the diagnosis of fungal infection due to proven and clinical sepsis or necrotizing enterocolitis (NEC) (5). Risk factors such as total parenteral nutrition (TPN), intubation, and NEC were determined for most of the patients (Table II). With the exception of three patients at the time of diagnosis, enteral nutrition had commenced for the remaining patients within the first week of life. All patients received parenteral nutrition from day 8 through to the 42 day. The diagnosis of NEC was made in 12 patients, with only two patients undergoing surgery. A central catheter was used in eight patients, and two patients had positive cultures, having been obtained concurrently from their catheters and the blood stream. After having established the diagno-

Table I. Clinical charesteristics of patients.

Patient	GA (weeks)	Birth weight	Gender	Delivery	Day of diagnosis	Clinical data	Bacterial sepsis	Antibiotic duration	Risk factors	Screening for Candida
1	26[5]	880	F	NSVD	8/15	PM, RDS, ICH	MRSE	8	TPN, I, FD, CC	–
2	26	1360	M	C/S	9/32	PM	MRSE, E. faeceum	9	TPN, I, FD, CC	Liver echogenity ↑
3	25[6]	940	F	C/S	70	PM, RDS, NEC	*S. aureus*, *S. hominis*	60	TPN, I, NEC	–
4	35[3]	1800	F	NSVD	12	PM, MAS	*K. pneumoniae*	12	TPN, NEC	–
5	28	1370	M	C/S	30	PM, RDS	–	30	TPN, I, FD, CC	Renal cortex echogenity ↑
6	30	1240	F	C/S	19	PM, RDS, NEC	Enterococcus	19	TPN, I, NEC, CC	Renal cortex echogenity ↑
7	28[3]	1220	F	C/S	35	PM, ICH, NEC	–	35	TPN, NEC, CC	Renal cortex echogenity ↑
8	30	1150	M	NSVD	58	PM, NEC	–	27	TPN, I,NEC ,CC	Renal cortex echogenity ↑
9	31[2]	1290	M	C/S	24	PM, NEC	MRSE	24	TPN, NEC (surgery)	–
10	33	1720	F	C/S	23	PM, NEC	MRSE, *K. pneumoniae*	23	TPN, I, NEC	–
11	28[2]	1340	M	C/S	34	PM, ICH,	Pol. kidney, *E. coli*	24	TPN, I, NEC	
12	31	1230	F	C/S	15	PM, RDS, NEC, PNX	–	5	TPN, NEC	–
13	29	1120	M	C/S	32	PM, RDS, NEC	S. mitis	32	TPN, I, NEC	–
14	30	1060	M	C/S	22	PM, SGA	Koag(-) staphylococcus	22	TPN, I, NEC, CC	–
15	25[4]	800	M	NSVD	8	PM, RDS	*S. capitis*	8	TPN, I, CC	Intracardiac trombus
16	29[1]	1440	F	NSVD	19	PM, NEC	MRSE	19	TPN, NEC (surgery)	–
17	31	1320	F	C/S	44	PM, RDS, PNX	*S. salivarus*	44	TPN, I, BPD(steroid)	–

GA: gestational age, F: Female, M: Male, NSVD: Normal spontaneous vaginal delivery, C/S: cesarean section, PM: prematurity, RDS: respiratory distress syndrome, ICH: intracranial hemorrhage, NEC: necrotising enterocolitis, PNX: pneumothorax, MRSE: meticillin resistant staphylococcus epidermidis, TPN: total parenteral nutrition, I: intubation, FD: feeding difficulties, CC: central catheter, BPD: bronchopulmonary dysplasia.

sis of fungal infection, all the central catheters were removed, and peripheral access was used for TPN solutions. One patient was on steroid therapy for bronchopulmonary dysplasia (BPD), which is a risk factor for fungal infection.

Early diagnosis and treatment follow-up can be made using CRP. The mean levels were respectively, 47.6 pg/ml and 35.5 mg/L for interleukin-6 (IL-6) and CRP. The mean and standard deviation of hemoglobin and white blood cell counts at the time of diagnosis were 10.9 ± 2.6 g/dL and 16,300 ± 8,900/μL, respectively. Eight patients had thrombocytopenia with a platelet count of < 100,000/μL; five of 8 patients had a platelet count of < 50,000/μL. Seven patients had hyperglycemia (> 125 mg/dl glucose levels).

Culture results indicated the presence of *Candida albicans* in 14 patients (and in the urine of one patient); *Candida pellucida*, *Candida guillermondi*, and a non-albicans *Candida* in one patient. All *Candida* species were susceptible to amphotericin B, and one species was resistant to fluconazole.

Due to the susceptibility of the *Candida* species, we initially used liposomal amphotericin B for all patients as first-line therapy. The reasons for modifying antifungal therapy only were "partial responselessness" (12 cases), "No response" (three patients), and severe renal tubular acidosis due to amphotericin treatment and "partial responselessness" (one patient). Seven patients had retinopathy of prematurity (ROP). The levels of ROP were 1 or 2, and no patient underwent surgery.

In Table II, we have presented the duration of antifungal treatments as alone (previous antifungal duration if the patient's treatment continued with voriconazole after discontinuing the previous antifungal), the day when the drug began to be given in combination (if patient took two antifungal drugs together as a previous antifungal and voriconazole and then the previous antifungal was stopped). In five patients, voriconazole was combined with amphotericin B. The dose regimen of voriconazole treatment varied from 2.5 mg/kg to 12 mg/kg twice daily (Table II), with majority of the patients receiving 6 mg/kg twice daily. We started with lower dosages due to the limited knowledge on the dosage regimen, adverse affects, and raised the initial dose when the patients were in a critically ill state. The mean, minimum, and maximum treatment durations were 15, 2, and 42 days, respectively 10 patients had a minimum treatment duration of 3 weeks (Table II). During the course of the disease, acute renal insufficiency was diagnosed in two patients. Transaminase monitoring was performed in all patients, which revealed no abnormality. The monitoring of liver toxicity revealed cholestasis in two patients. Amphotericin B was given in combination with voriconazole to the first patient after 11 days and the second patient after 3 days. Both patients were discharged, with no cholestasis apparent at the time of discharge.

In the end, 11 patients were cured. Two patients who underwent voriconazole therapy for only 2 and 6 days, respectively, died. Two patients were transferred to another hospital due to surgical problems.

Discussion

Voriconazole is a triazole antifungal agent with a broad spectrum of activity and a good safety profile. It demonstrates excellent potency against both flamentous and yeast organisms and has been used to treat sepsis caused by *Candida* species, including fluconazole-resistant *Candida albicans*[8-9]. Administered orally (in which complete absorption occurs) or intravenously, voriconazole is extensively distributed throughout tissues and is predominantly metabolized by the cytochrome P450 2C19 (CYP2C19) oxidase system. Dose adjustments are necessary in patients with chronic hepatic impairment[10]. In individuals with renal dysfunction, no dose adjustments are needed for oral voriconazole, which is metabolized by the liver, whereas such adjustments are required for the intravenous formulation, which is excreted through the kidney. Elevated transaminase levels (13.8%), rash (13.8%), abnormal vision (5.1%), and photosensitivity reactions (5.1%) have been the most common treatment-related adverse effects[10].

The number of case reports in the neonatal literature on voriconazole use, treatment response, and adverse effects, is limited. Muldrew et al.[11] reported on the use of intravenous voriconazole to treat a pre-term infant born with at a gestational age of 27 weeks for a disseminated infection due to fluconazole-resistant *Candida albicans*. The 14-day-old infant received liposomal amphotericin B for 52 days and a combination of liposomal amphotericin B and voriconazole for 19 days. Voriconazole at a dose of 6 mg/kg was administered every 8 hours with no side effects[2-4]. Santos et al[12] also used intravenous voriconazole to treat a pre-term infant born at a gestational age of 24 weeks for cutaenous aspergillosis. The 10-day-old infant received a combination of liposo-

Table II. Microbiologic and treatment charesteristics of patients.

Patient	Fungus type	Previous antifungal (alone/combine day)	Cause of voriconazole beginning	IL-6/CRP (pg/ml-mg/L)	Glucose (mg/dL)	Dose (mg/kg, BID)	Duration (day)	Cause of discontinuation	Complication	Prognosis
1	*C. guillermondi/ C. albicans*	Amp. B/15/-	PaR	319/48	220	5	29	No response	No	Discharged
2	*C. albicans*	Amp. B/9/-	PaR	14/38.9	195	7 (loading), 3	23	No response	No	Discharged
3	*C. albicans*	Amp. B/5/7	PaR	2.5/26	100	3	11	Cure	No	Discharged
4	*C. albicans*	Amp. B/8/-	Renal tubular acidosis and PaR	38.2/38.5	185	3	7	Transferred	No	Transferred
5	*C. albicans*	Amp. B/12/3	PaR	24/32	117	12 (loading), 6	15	Transferred	No	Transferred
6	*C. albicans*	Amp. B/13/-	PaR	155/38.8	171	10	21	Cure	No	Discharged
7	*C. albicans*	Amp. B/4/ 11	NoR	14.9/30.4	98	12	26	Cure	Cholestasis	Discharged
8	*C. albicans* (urine)	Amp. B/6/-	PaR	3.3/32.1	85	10	42	Cure	No	Discharged
9	*C. albicans*	Amp. B/8/-	PaR	23.4/36.4	76	6 (loading), 3	16	Cure	No	Discharged
10	*C. albicans*	Amp. B/4/-	PaR	11/36	213	4 (loading), 2	5	Cure	No	Discharged
11	*C. pellucida*	Amp. B/14/-	PaR	11.7/43.6	173	2.5	6	Exitus	No	Exitus
12	*C. albicans*	Amp. B/13/-	NoR	12.9/37.2	85	3	15	Cure	No	Discharged
13	*Non.albicans C.*	Amp. B/8/3	PaR	16.8/32.7	75	6.5 (loading), 3.5	14	Cure	Cholestasis	Discharged
14	*C. albicans*	Amp. B/11/11	NoR	102/35.5	202	10	11	Cure	Liver function abn.	Discharged
15	*C. albicans*	Amp. B/9/9	PaR	20.5/31	97	6	30	Cure	No	Discharged
16	*C. albicans*	Amp. B/8/-	PaR	16/36.2	74	6	2	Exitus	No	Exitus
17	*C. albicans*	Amp. B/18/-	PaR	25/30.5	112	6 (loading), 3	7	Cure	No	Discharged

Amp. B: amphotericin B, CRP: C-reactive protein, IL-6:Interleukin-6, PaR: partial responselessness, NoR: no response, Previous antifungal alone day:Other antifungal before voriconazole, Previous antifungal combine day: Days of both the other antifungal and voriconazole if used together we gave the duration of antifungal treatments as alone (previous antifungal duration if patient's treatment continued as voriconazol after discontinued previous antifungal), combine day (if patient took two anfifungal drugs together as previous antifungal and voriconazole and than previous antifungal stopped).

mal amphotericin B and micafungin as well as 7 weeks of intravenous voriconazole at a dose of 4 mg/kg twice daily. The patient had ROP, possibly resulting from the effect of voriconazole therapy on retinal development[2-4]. Kohli et al[13] reported two cases in which they used voriconazole[2-4]. In the first case, the patient had tachycardia-induced cardiomyopathy and a *Candida pelliculosa* infection. Ten days after discharge, amphotericin B therapy was replaced with oral voriconazole at a dose of 4 mg/kg twice daily for a total of 2 weeks; no side effects were noted. In the second case, the patient had congenital heart disease along with a *Candida* species infection. After persistent thrombocytopenia while taking liposomal amphotericin B for 10 days, therapy was modified to oral voriconazole at a dose of 4 mg/kg twice daily. Oral treatment was discontinued after 3 weeks, and no side effects occurred.

No acceptable voriconazole dose for neonates has been identified. Therefore, we used case reports of newborn patients and dose recommendations for children to determine the voriconazole dosage. Doses of 8 to 24 mg/kg/day have been used for newborn patients in case reports. A loading dose of 4 to 6 mg/kg and a maintenance dose of 2 to 3 mg/kg twice a day were used in our study. Most of the patients had treatment durations of a minimum of 21 days. There was no consensus on the treatment duration. The dose was increased according to CRP levels, culture results, and the patient's clinical characteristics.

The possibility of voriconazole's causing visual problems is well known. Seven patients had ROP; the degrees of ROP were 1 or 2 and no patient underwent surgery. Despite the fact that no defined relationship between voriconazole and ROP have been observed, and although many risk factors have been identified (e.g., prematurity, sepsis, intubation and NEC). ROP may be attributable to voriconazole therapy in the seven patient in the present study.

For our patients, voriconazole therapy proved to be successful, with no life-threatening side effects. Most patients were cured in spite of a lower dose of voriconazole compared with other successful reports, and the size of our study population exceeds all others in the neonatal literature.

Conclusions

Voriconazole at this dosage common with other antifungal agents or alone appears to be a safe and effective antifungal agent for neonatal invasive neonatal FS. Further studies are required to learn the pharmacokinetics (e.g., serum half-life, concentration, time of peak concentration, and distribution) of voriconazole in newborns.

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