FLUCONAZOLE THERAPY IN NEONATAL SYSTEMIC CANDIDIASIS
Yenidoğan sistemik kandidiazisinde flukonazol tedavisi

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Summary: *Seven infants with a mean birth weight of 1.87± 0.18 kg and a mean gestational age of 34 1.0 weeks developed systemic candidiasis. All these infants had required prolonged peripheral intravascular catheterization, broad-spectrum antibiotic therapy and hyperalimentation prior to the development of systemic candidiasis. Candida species were isolated from the blood of all infants. The most frequently observed clinical features were abdominal distention, temperature instability and hypotonia. Intravenous fluconazole eradicated the systemic infection in five of seven infants without any side effects. We conclude that infants with neonatal systemic candidiasis can successfully be treated with fluconazole.*

Key Words: *Fluconazole, Candidiasis, Infection*

Özet: *Ortalama doğum ağırlığı 1.87±0.18 kg ve ortalama gestasyonel yaşı 34±1.0 hafta olan yedi yenidoğanda sistemik kandidiazis gelişti. Tüm bu olgulara sistemik kandidiazis gelişmeden önce uzun süreli periferik intravaskuler kateterizasyon, geniş spektrumlu antibiotik tedavisi ve hiperalimantasyon uygulanmıştı. Tüm olguların kan kültürlerinde Candida üretildi. En sık gözlenen klinik bulgular; abdominal distansiyon, ısı regulasyonunda bozukluk ve metabolik asidoz idi. İntravenöz flukonazol, hiç bir yan etki görülmeksizin, yedi olgunun beşinde sistemik enfeksiyonu eradike etti. Neonatal kandidiazisli olgular flukonazol ile başarılı bir şekilde tedavi edilebilir.*

Anahtar Kelimeler: *Flukonazol, Kandidiazis, Enfeksiyon*

Despite the improvement in survival rates of very low birth infants, systemic candidiasis remains as an important contributing factor to neonatal morbidity and mortality in the neonatal intensive care units (NICU) (1,2). The predisposing factors that have been suggested as major determinants in the development of candidiasis are prematurity, prolonged intravascular catheterization, hyperalimentation, prolonged endotracheal intubation and use of broad-spectrum antibiotics (1,2,3).

Treatment of these fungal infections usually requires amphotericin B, which is potentially nephrotoxic (4).

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There is therefore a need for a less toxic antifungal agent. In this study we chose fluconazole as first line antifungal therapy, since it is known to possess good fungistatic activity and less toxicity than amphotericin B. At the same time we analyzed the diagnostic features, clinical presentations and other therapeutic regimens.

MATERIAL AND METHODS

Seven infants with documented systemic fungal infection in the NICU of Gülhane Military Medical Faculty Hospital, Ankara, from January 1994 to June 1995 were included in the study. Informed consent was obtained from the parents before infants entered into the study.

Data on seven infants with systemic candidiasis are summarized in table I. The gestational ages were

between 30 and 38 weeks and birth weights were between 1250 and 2600 g. Mean birth weight was 1.87±0.18 kg and mean gestational age was 34.0 ±1.0 weeks. Five of six preterm infants had hyalen membran disease and required assisted ventilation. The only full-term infant in the study had perinatal asphyxia and gastrointestinal bleeding.

Major risk factors for neonatal systemic candidiasis in the study group are shown in table II. The most frequently observed risk factors were prolonged intravascular catheterization, prematurity, broad-spectrum antibiotic therapy and prolonged hyperalimentation.

In four of the seven infants who had received broad-spectrum antibiotics, the antibiotherapy was started at least 72 hours before the documentation of systemic candidiasis and the remainder two had received antibiotics before.

Blood, urine, cerebrospinal fluid and gastric aspirate specimens from all infants were collected for cultures for infection screening. Other biochemical studies (blood urea nitrogen, creatinin, electrolytes, liver enzymes, glycemia) were performed in all cases.

Fluconazole 6 mg/kg initially and after 24 hours a maintenance dose of 3 mg/kg/day was administered with a constant one hour intravenous infusion. Amphotericin B was used with a daily dose of 1 mg/kg. All the cases received oral nystatin for eradication of gastrointestinal Candida colonization.Cure was defined as clinical and laboratory improvement and sterilization of cultures. Four cases were already receiving antibiotics for the documented bacterial infections or sepsis before the diagnosis of systemic candidiasis was made.

RESULTS

The mean age at onset of systemic fungal infection was 9.5±2.1 days. The mean time between the onset of clinical symptoms and initiation of antifungal therapy was 3.0±0.7 days. Total white blood cell counts of 18000/mm3 in five cases and shift to left in all cases were noted. The ratio of immature leukocytes to the total was 0.2 in all cases. Thrombocytopenia (defined as 150000/mm3) was present in five cases.

Candida species organisms were isolated from the peripheral blood of all cases. Only in one case urine and gastric aspirate cultures were also positive for Candida.

Table III shows clinical features of systemic candidiasis. Abdominal distention, temperature instability and hypotonia were the most frequently recorded features.

Table IV shows the antifungal therapy in infants with systemic candidiasis. The initial treatment in all babies was with fluconazole. Only in two cases who did not respond to fluconazole therapy, amphotericin B was used as a second line antifungal therapy at the ninth and 12th days of fluconazole therapy. In both therapy regimens drugs were administered by intravenous route.

No clinical or laboratory signs suggested toxicity. Serum creatinine, total and direct bilirubins, alkaline phosphatase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, hemoglobin and leukocyte count with differential, platelet and reticulocyte count were determined at least weekly in all cases receiving treatment.

All the cases survived after cessation of antifungal therapy and there have been no recurrences or any evidence of sequela attributable to candidiasis.

Table I. Data on seven infants with systemic candidiasis

Patient No	Birth Weight (g)	Gestational Age (w)	Medical Diagnosis	Clinical Signs	Laboratory Findings
1	1250	30	Prematurity, RDS	Bile stained vomiting, NEC like syndrome	Shift to left, Leucocytosis
2	1600	34	Prematurity, RDS	Increasing oxygen requirement	Shift to left, Leucocytosis, Thrombocytopenia CRP (+)
3	2300	36	Prematurity	Lethargy, Hypotonia, Increasing oxygen requirement	Shift to left, Leucocytosis, Thrombocytopenia
4	1730	35	Prematurity	Heat instability, Acidosis, Apnea and bradycardia, NEC like syndrome	Shift to left, Leukocytosis
5	2130	34	Prematurity, RDS	Heat instability , Acidosis. Lethargy, Hypotonia, NEC like syndrome	Shift to left, Thrombocytopenia
6	1480	31	Prematurity, RDS	Lethargy, Heat instability, NEC like syndrome	Shift to left, Thrombocytopenia, CRP (+)
7	2600	38	Perinatal sphyxia, Gastrointestinal bleeding	Heat instability	Shift to left, Leukocytosis, Thrombocytopenia

Table II. Risk factors in seven infants with systemic candidiasis

Risk factors	Rate %
Peripheric intravascular catheterization	100
Prematurity	85
Broad-specturm antibiotherapy	85
Hyperalimentation	71
Local disease (oral)	57
Aminophylline therapy	28

Table III. Clinical features in seven infants with systemic candidiasis

Clinical signs	Rate %
Abdominal distention	57
Heat instability	57
Lethargy	43
Hypotonia	29
Bile stained vomiting	29
Increasing oxygen requirement	29
Apnea and bradycardia	14

Tablo IV. Antifungal therapy in seven infants with systemic candidiasis

Patient No	Day treatment commenced	Agent	Duration of therapy(days)	Positive culture sites	Other antifungal therapy
1	23	Fluconazole	12	Blood, Urine, Gastric aspirate	Oral (nystatin)
2	21	Fluconazole	8	Blood	Oral (nystatin)
3	11	Fluconazole	7	Blood	Oral (nystatin)
4	5	Fluconazole	18	Blood	Oral (nystatin)
5	12	Fluconazole Amphotericin B	12 14	Blood	Oral (nystatin)
6	11	Fluconazole Amphotericin B	9 34	Blood	Oral (nystatin)
7	12	Fluconazole	17	Blood	Oral (nystatin)

DISCUSSION

Systemic candidiasis is observed with an increasing incidence in high risk neonates (1). Although it can be seen as isolated cases or transient candidemia, it can cause more severe complications like meningitis, ventriculitis, renal abscess, artritis or osteomyelitis (3,5). Clinical presentation and laboratory findings are not always specific enough to differentiate the bacterial infections from the fungal ones (2,3).

High rates of mortality (25%-50%) and morbidity (25%) associated with systemic candidiasis in neonates have been attributed to diagnostic delays and therapeutic difficulties (6). Neonates who will develop systemic candidiasis may be predicted by the evolution of some risk factors (1). In our study we found that peripheral vascular catheterization was the most prominent risk factor. It may be the major source for the Candida to spread into the systemic circulation (7). Very low birth weight (VLBW) infants are reported to be another risk group (3,8). In our study group six of seven infants were premature with a mean gestational age of 33.3± 0.9 weeks. On the other hand the major risk for term newborns is gastrointestinal bleeding; hence the invasion of injured mucosa with Candida may cause systemic candidiasis (9). Aminophylline therapy for the apnea of prematurity may also be associated with systemic candidiasis by the inhibition of anticandidicidal activity of granulocytes (10). The use of broad-spectrum antibiotics and hyperalimentation are also associated with the development of Candida infections (7,11).

It is reported that the development of systemic candidiasis usually occurs at the fourth week of life (3,6,7). In our study group it was 9.5± 2.1 days and this may be attributed to the early administration of the broad-spectrum antibiotics.

Confirmation of systemic candidiasis is difficult. The documentation of Candida in blood culture is essential for the diagnosis. Other laboratory findings; leukocytosis, shift to left, thrombocytopenia may also support the diagnosis (7). Hundred percent of the infants had shift to left, 71% had

thrombocytopenia and 71% had leukocytosis in our study group and all these parameters returned to normal levels in the fourth day of treatment and this could be accepted as a sign of good response.

Many reports suggest that all candidemic neonates should be treated with amphotericin B and 5-fluorocytosine which are potentially toxic agents (12,13). Fluconazole which is less toxic than amphotericin B is selected here although there is limited experience in neonates with this drug (14,15). Fluconazole is known to possess good fungistatic activity. Optimal duration of therapy for systemic candidiasis with any antifungal drug remains unclear (16,17). Clinical and laboratory improvement and the sterilization of affected sites is important for determining the duration of therapy (7). In our study group resolution of the clinical symptoms and two subsequent negative cultures were accepted as sufficient criteria for termination of the therapy. Duration of therapy for the neonates treated with fluconazole was 12.4 ±10.1 days and with amphotericin B it was 24.0±10,1 days. We feel that fluconazole requires a short duration of therapy, although it may not be appropriate to compare fluconazole with amphotericin B as such.

Prevention of gastrointestinal tract and skin from Candida colonization in susceptible neonates is difficult. To reduce the colonization of these sites, we used oral nystatin and antiseptic solutions to the puncture sites but four neonates who had received the prevention procedures at least 48 hours before the documentation of systemic candidiasis still developed the disease.

It is reported that mortality in neonatal systemic candidiasis is between 12%-64% (6,7,13). All of our cases survived with the appropriate and early therapy.

As conclusion, in deteriorating neonates despite the appropriate antibiotic therapy, fungal infection should be considered in the presence of high risk factors. Based on our particular experience, fluconazole could be used for the treatment of neonatal systemic candidiasis with confidence.

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