CASE REPORT

Serum Amphotericin B Concentration in a Very Premature Infant with Disseminated Candidiasis

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Abstract

A 1,040-g premature baby was diagnosed to have disseminated candidiasis and treated with amphotericin B (AMB) and 5-fluorocytosine. During the treatment, an unexpectedly large dose of AMB was infused unintentionally. AMB level was as high as 1.73 $\mu\text{g/mL}$ soon after 5 mg/kg infusion instead of 0.5 mg/kg. However, it dropped rapidly to 0.83 $\mu\text{g/mL}$ after 24 hours. AMB was detected in patient's serum at a higher level than minimal inhibitory concentration as long as one month after treatment was stopped. The patient showed liver dysfunction but no nephrotoxicity. The further studies are needed to establish safe and effective treatment regimen in premature infants with disseminated candidiasis.

Key words: amphotericin B, disseminated candidiasis, premature infant

Introduction

In recent years, neonatal disseminated candidiasis has been diagnosed with increasing frequency, and has become a serious threat to premature babies. Past studies have predominantly dealt with the incidence, predisposing factors, and other clinical

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features of this condition.¹⁻⁴ Although amphotericin B (AMB) is most frequently used for the treatment of neonatal disseminated candidiasis, little is understood about its pharmacokinetics in neonates.

We present a case report of a very premature infant with disseminated candidiasis, in whom serum concentrations of AMB were determined serially after an accidentally large dose had been infused.

Case Report

A 1,040-g male neonate, born after a spontaneous labor during the 26th week of gestation, was admitted to the neonatal intensive care unit of [REDACTED] immediately after delivery. Initial management included intratracheal intubation, placement of an umbilical arterial catheter, and mechanical ventilation. Since the amniotic fluid was meconium-stained, and he was born 63 hours after rupture of membranes, cefotaxime (CTX) was started for suspected sepsis. On the 33rd day, he suddenly developed frequent apnea. Sepsis was strongly suspected and he was treated with CTX and gentamicin (GM). With aminophylline infusion, the frequency of apnea decreased. Stool culture at this point revealed *Candida albicans*, but urine and blood cultures were negative. White blood cell count was 14,200/mm³, and C-reactive protein (CRP) was negative.

On the 41st day, the patient again showed frequent apnea. There were some petechiae on his bilateral lower extremities. No enanthem was found. The patient's abdomen was markedly distended. While blood cell count was 8,300/mm³ and platelet count was 60,000/mm³. CRP was 3+. Ampicillin (AMPC) was added to the treatment. On the 45th day, a blood culture obtained on the 42nd day revealed *C. albicans*. Urine was not cultured. The cerebrospinal fluid contained 14/mm³ lymphocytes. The glucose and protein levels in the cerebrospinal fluid were within normal limits, and culture was negative. *Candida albicans* was also cultured from the tip of the umbilical arterial catheter.

A diagnosis of disseminated candidiasis was made, and treatment with AMB and 5-fluorocytosine (5-FC) was started at once.

One hundred and fifty mg/kg of 5-FC was given through a nasogastric tube for 4 days, but it was discontinued because of increased gastric residuum and abdominal distension. It was started again at 75 mg/kg/day on the 53rd day.

AMB was initiated at 0.1 mg/kg/day infused over 3 hours, and was increased over a period of 7 days to an intended maximum daily dose of 0.5 mg/kg. The patient received 0.5 mg/kg/day of AMB for 4 days. Although slight hyponatremia (129 mEq/L) was noted, this was corrected with parenteral supplementation. Liver functions were normal during this period.

On the 56th day, 5 mg/kg of AMB instead of 0.5 mg/kg was infused unintentionally.

tionally. Both AMB and 5-FC were discontinued immediately, and evaluation of AMB serum concentration was started.

Total bilirubin level was elevated from 2.0 mg/dL to 5.5 mg/dL on the following day, and both total and direct bilirubin levels continued to increase until the 65th day, with peak levels of 9.5 and 8.7 mg/dL, respectively.

Serum-GOT level was 46 mU/mL and S-GPT level was 17 mU/mL prior to 5 mg/kg infusion. Immediately after that, S-GOT was 118 mU/mL, and S-GPT was 29 mU/mL. On the 60th day, a test dose of 0.1 mg/kg of AMB was injected, but because liver functions worsened (S-GOT 279 mU/mL, and S-GPT 51 mU/mL), the treatment was discontinued after one dose. As a result, the patient received a total of 7.2 mg of AMB and approximately 900 mg of 5-FC.

During and after therapy, the values of serum creatinine and blood urea nitrogen did not show any abnormality. White blood cell count and platelet count returned to normal on the 60th day, and CRP remained negative after the 66th day. Subsequent cultures did not show any *C.albicans* growth. The patient showed liver dysfunction and jaundice of the intrahepatic obstruction type for more than 3 months. The ultra-

Table 1 Serum Concentration of Amphotericin B

1) Time after 5 mg/kg IV	Serum concentration (μ g/ml)
3 hours	1.73
8 hours	1.32
1 day	0.83
2 days	0.57
3 days	0.23
4 days	0.19
5 days	0.16
2) Time after 0.1 mg/kg IV	Serum concentration (μ g/ml)
30 minutes	0.50
1 hour	0.41
2 hours	0.35
3 hours	0.30
1 day	0.56
9 days	0.30
16 days	0.47
24 days	0.43
30 days	0.45
44 days	<0.10

MIC: 0.2 μ g/ml

sonography did not show liver abscesses or any signs of fatty liver. He is now 12 months old and developing normally.

Monitoring of serum AMB concentration

The Table and Figure show the serum concentrations of AMB determined by high pressure liquid chromatography (HPLC).⁵ The minimal inhibitory concentration (MIC) for cultured candida was 0.2 $\mu\text{g/mL}$.

Three hours after infusion of the unexpectedly large dose, AMB serum concentration was as high as 1.73 $\mu\text{g/mL}$. It then fell rapidly to 0.83 $\mu\text{g/mL}$ in the first 24 hours, and had already reached 0.19 $\mu\text{g/mL}$ by the 4th day. It again reached 0.5 $\mu\text{g/mL}$ immediately after infusion of the test dose of 0.1 mg. Three hours later, it had decreased to 0.3 $\mu\text{g/mL}$, and thereafter, AMB was present in the patient's serum at a higher level than MIC for as long as one month.

Fig. 1 Serum concentration of amphotericin B after 5 mg/kg dose, showing a rapid fall in the first few hours and dropping more slowly in the subsequent phase.

Discussion

Ward⁶ reported that a significant concentration of AMB was detected in the serum of 800-g infant as long as 17 days after completion of treatment. To our knowledge, this is the only report on AMB serum concentration in a premature infant. In the present case, we determined the changes in serum AMB levels by serial sampling after therapy.

Although the serum AMB concentration increased immediately after infusion, it declined rapidly to a steady level within the first few hours. It then decreased more slowly over the next few days, and AMB remained at a significant level for about one month.

A similar change in AMB serum concentrations has been observed in adults by Atkinson.⁷ He reported that the terminal elimination half-life of AMB was approximately 15 days, and explained its characteristic pharmacokinetics in terms of three-compartment theory. When infused into the central (intravascular) compartment, AMB is distributed into both the rapidly equilibrating peripheral compartment (liver, spleen, and intestine) and slowly equilibrating peripheral compartment (skeletal muscle and skin). The initial rapid elimination is from the central and rapidly equilibrating compartments. When treatment is stopped and concentration becomes low in the central compartment, AMB gradually returns from the slowly equilibrating peripheral compartment, contributing to the long terminal elimination phase. The pharmacokinetics of AMB in very premature infants can be described in terms of this three-compartment theory.

The dose levels and intervals frequently recommended in the literature are not based on pharmacokinetic studies. Because of the rapid elimination from the serum in the first few hours, it is possible that the initial low dose of AMB is unable to achieve effective serum concentration. A higher dosage, or more frequent injections might therefore be necessary for the urgent establishment of effective therapy.

Two recent reports^{2,3} have reached opposite conclusions about the safety of AMB in premature infants. Johnson³ reviewed 21 low-birth-weight babies who received AMB, and concluded that the drug was well tolerated. On the other hand, Baley² reported nephrotoxicity in 7 out of 10 babies, and 6 of these infants showing drug toxicity died. However, neither of these two reports evaluated the serum concentrations of AMB. In order to determine the toxic level and establish a safe form of treatment, there is clearly a need for detailed pharmacokinetic and toxicity studies of AMB in premature infants.

5-FC also present some toxicity in adults. Bone marrow suppression, gastrointestinal toxicity and disturbed hepatic function were observed in some patients, but these were mild and reversible when the dosage was decreased and serum concentration

was lowered.⁸ Side effects of 5-FC in premature infants are not fully studied.

The hepatic dysfunction observed in our patient is of considerable concern. Although Baley² found hepatic necrosis in some of their cases at autopsy, he considered that it might have been secondary to the prolonged usage of total parenteral nutrition. Our patient was not receiving parenteral alimentation.

The possibility of 5-FC being the causative agent for liver dysfunction is low, since it was discontinued once and restarted at half of the recommended daily dosage. The serum concentration of 5-FC was not measured, but it must have been lower than the toxic level. Hepatic dysfunction occurred soon after infusion of an unexpectedly large dose of AMB, and worsened after additional AMB infusion. Therefore, it seems more reasonable to suspect AMB as the causative agent.

The most important aspects of treatment of neonatal disseminated candidiasis are the early initiation of effective treatment and the minimization of drug toxicity. Therefore, the dosage, intervals, and length of therapy should be individualized in each case, with careful monitoring of the serum concentrations of AMB.

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