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Neonatal systemic candidiasis treated with miconazole

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SUMMARY Two premature newborn infants with systemic candidiasis are reported; both were treated with miconazole. One died and the other made a complete recovery. Miconazole may be a useful addition to the drugs available for the treatment of systemic candidiasis in the neonate, but all of them have serious limitations.

Systemic candidiasis is recognised as a potential hazard in premature newborn infants receiving intensive care. Effective treatment can be given for this condition, and it is therefore important to make the diagnosis early. This paper reports 2 infants; both were treated with miconazole but one died.

Case reports

Case 1. A boy, birthweight 950 g, was born preterm in the antenatal ward in January 1979. His mother had been given dexamethasone and salbutamol since her admission in premature labour 4 days earlier. Gestational age was estimated at 27 weeks, and the baby was transferred to Hammersmith Hospital 4 hours after birth.

He developed clinical and radiological evidence of hyaline membrane disease. The first examination showed no other abnormality, although subsequent abdominal palpation suggested the possibility of a horseshoe kidney. An umbilical arterial catheter was inserted to monitor blood–gases, which remained satisfactory in ambient oxygen concentrations below 60%.

At age 8 hours the baby started having apnoeic attacks. Initial investigations did not suggest an underlying cause other than immaturity. He was treated with penicillin and gentamicin for 7 days. Continuous positive airways pressure (CPAP) proved unhelpful, but continuous intravenous infusion of aminophylline resulted in considerable diminution of the frequency and severity of his apnoeic attacks.

He was fed intravenously via Silastic central venous cannulas from 5 to 34 days of age. Nasojejunal feeds were introduced at 11 days, but were stopped at 14 days because of recurrence of apnoeic attacks. At this stage there was hypercapnia, associated with excessive tracheal secretions, and the baby received respiratory assistance, in the form of intermittent positive pressure ventilation (IPPV) and CPAP, from 16 to 24 days of age. A second course of penicillin and gentamicin was given for 11 days. *Staphylococcus epidermidis* and *Streptococcus viridans* were isolated from a pharyngeal swab on day 24, but no pathogens were isolated from repeated blood cultures, the Silastic cannula tip, cerebrospinal fluid (CSF), or urine specimens.

Thereafter progress was satisfactory until the 29th day, when, during the introduction of a nasojejunal tube, he again had an apnoeic attack, and he appeared pale and inactive. Investigations showed: haemoglobin 10·5 g/dl, WBC $29{\cdot}5 \times 10^9$/l (71% neutrophils, 7% bands). CSF contained 4 RBC and 20 WBC $\times$ 10^6/l, but no organisms were seen or cultured. Blood cultures yielded *S. epidermidis* from one bottle and nonhaemolytic streptococcus from one bottle.

He was given a third course of penicillin and gentamicin, and his condition improved. Nasojejunal feedings were introduced gradually, until by day 34 he was entirely milk fed and the central venous feeding cannula could be removed. *S. epidermidis* was subsequently cultured from the catheter tip.

From day 30, urine microscopical examination showed budding yeast cells and hyphae, and urine cultures yielded *Candida albicans*. Treatment with miconazole was started on day 34 (Table), but 12 hours later he developed pronounced abdominal distension. An *x*-ray film of the abdomen showed gas in the portal system, and at 35 days he died of fulminating necrotising enterocolitis.

At necropsy, the main abdominal findings were acute necrotising enterocolitis, and a horseshoe kidney with mycelial masses in the renal pelvis and multiple abscesses in the medulla. In the brain, there were multiple granulomata, containing a few hyphae (Figure) within the white matter, especially in the periventricular region. No other organ appeared to be affected.

Case 2. In January 1979 a girl, birthweight 1200 g, had birth asphyxia after a vertex delivery at 29 weeks' gestation. Her mother had received betamethasone, ritodrine, and ampicillin before delivery. After initial resuscitation the baby developed respiratory distress, and required IPPV from one hour after birth. An umbilical arterial catheter was

Table *Plasma miconazole levels*

	Dose (mg/kg)	*Route*	*Frequency (hours)*	*Predose (μg/ml)*	*Postdose (μg/ml)*		*MIC (μg/ml)*
					30 min	*2 hours*	
Case 1	5	IV	24	—	0·3	0·2	0·05
Case 2, 1st course							
After 6 days	4	IV	24	0·2	0·4	0·2	
Case 2, 2nd course							0·10
After 2 days	7·4	IV	12	0·1	0·4	0·2	
After 7 days	7·4	IV	12	0·2	0·4	0·3	
After 7 days	15	Naso-gastric tube	8	—	—	0·6	

IV=intravenous, MIC=minimum inhibitory concentration.
Plasma miconazole levels were determined by means of a broth dilution technique.[9]

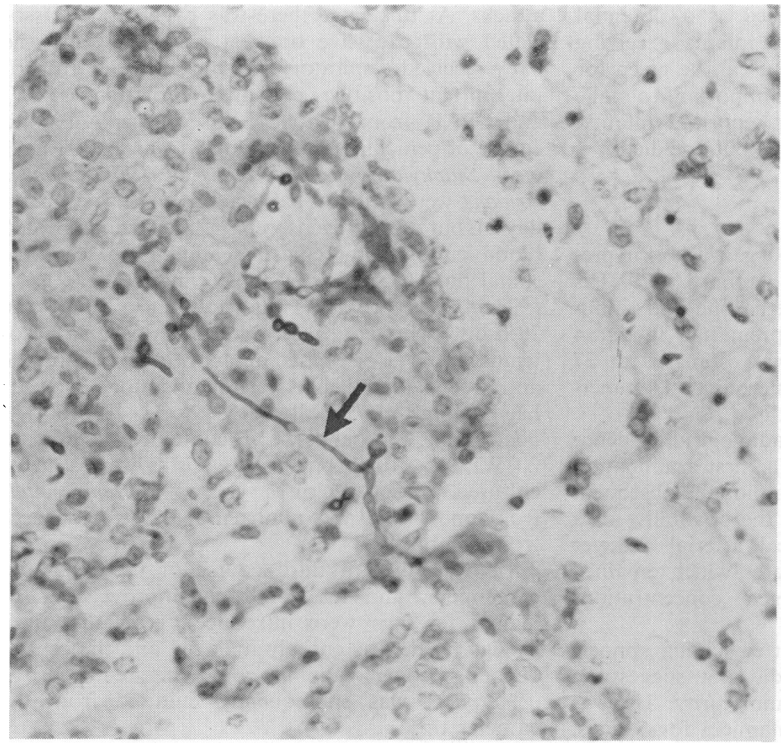

Figure *Granuloma in cerebral white matter containing fungal hyphae (arrowed). PAS × 400.*

inserted for blood–gas monitoring, and she was given penicillin and gentamicin. Amino-acid solutions and dextrose were given via the arterial catheter. At 53 hours the baby developed a left pneumothorax, and, because of difficulties in achieving sustained re-expansion of the left lung, she was transferred to Hammersmith Hospital at age 6 days.

Initially she made good progress, but because of continuing respiratory embarrassment, alimentation was continued via peripheral cannulas until day 14, and therafter via a Silastic central venous catheter. The pleural drain, from which *S. epidermidis* was subsequently isolated, was removed on day 10.

IPPV was stopped on day 11, but she continued to require extra oxygen, regular bronchial lavage, and physiotherapy because of excessive bronchial secretions, associated with recurrent bilateral lower lobe collapse, and hypercapnia. Cultures of tracheal aspirate yielded a mixed growth of *S. epidermidis* and *C. albicans*. On day 12 flucloxacillin was substituted for penicillin and gentamicin, without any improvement in her condition, and in view of further isolates of *Candida* sp. from the sputum, antibiotics were stopped on day 17.

On day 21 the baby started having frequent apnoeic attacks, for which she was treated with aminophylline. *C. albicans* was isolated not only from tracheal secretions, but also from the urine, in which budding yeasts were seen on microscopical examination. Blood cultures and CSF cultures were negative. Miconazole was given intravenously in a dose of 5 mg (4 mg/kg) daily, diluted in 5 ml 0·9% saline, and infused over one hour.

After 6 days' treatment, bronchial secretions had greatly diminished, urine microscopical examination showed no yeasts, and urine cultures were negative. The baby started to gain weight satisfactorily, her apnoea diminished, and miconazole and aminophylline were stopped after 8 days—on day 29.

During the next 6 days there was an insidious deterioration in her condition, with hypotonia, inactivity, and increasingly frequent apnoea. On day 32 the central venous cannula was removed, and parenteral alimentation was continued via peripheral veins.

On day 35 budding yeasts and hyphae were again seen in a urine specimen obtained by direct bladder aspiration, and *C. albicans* was isolated from one of three bottles in blood cultures taken 3 days previously. CSF examination was negative. Treatment with miconazole was restarted in the increased dose of 10 mg twice daily, intravenously. The baby's condition remained poor however until day 41, when *S. epidermidis* was isolated from blood cultures drawn 3 days previously, and she was given penicillin and gentamicin.

From then on she made excellent progress. Miconazole was given intravenously for 8 days and then via the nasojejunal tube for a further 9 days (Table). No side effects attributable to miconazole were observed, other than superficial ulcers secondary to phlebitis at peripheral infusion sites. No pathogens were isolated from these lesions, which healed rapidly, although with some scarring. Repeat examinations during the next 4 weeks showed no recurrence of yeasts in the urine. Ophthalmic examination on day 66 was normal.

At age 5 months, her growth and developmental progress are satisfactory, and there are no abnormal neurological findings.

Discussion

Systemic candidiasis is well recognised as a complication of parenteral nutrition, and of broad-spectrum antibiotic therapy in the sick preterm infant. Common presentations are with renal involvement,[1] meningitis,[2] osteitis, and arthritis. Endophthalmitis was present in 10% of the 49 reported cases reviewed by Keller *et al.*,[1] but the true incidence may be higher.[3]

Case 1 illustrates the fact that extensive cerebral involvement may occur without being clinically apparent. There were no symptoms to suggest this, and CSF cultures were negative on 5 occasions. Blood cultures and catheter tip cultures were also negative for *Candida* sp. Singer and Gilles[4] reported 7 necropsy cases of unsuspected *Candida* sp., meningoencephalitis, with negative CSF cultures at necropsy, all occurring in critically ill babies receiving parenteral alimentation and broad-spectrum antibiotics. They pointed out the predominance of deep parenchymal lesions (microabscesses, cerebritis, and vasculitis) which are not reflected by CSF abnormalities.

Stone[5] has suggested that urine examination and cultures may offer a more reliable means of diagnosing systemic candidiasis than venous blood culture, and these cases support this view. We now consider that regular urine examination should be part of the routine management of preterm infants receiving parenteral alimentation, and that the finding in the urine of budding yeast cells, particularly hyphae,[6] should be considered an indication for immediate antifungal chemotherapy. Ideally, parenteral feeding should be stopped and intravenous cannulas removed, but this may not always be practicable in the very small, sick, premature infant.

We are not aware of any other reports of the use of miconazole to treat preterm infants with systemic candidiasis, but in view of the potential toxicity of

amphotericin, and the frequency and rapidity with which resistance to 5-fluorocytosine may develop during treatment, it may prove to have a place in their management.

Miconazole is a synthetic imidazole derivative, which alters the permeability of fungal cell membranes. Although soluble in most organic solvents, it is only slightly soluble in water, and circulating miconazole is mainly albumin bound. It penetrates poorly into cerebrospinal fluid, and hardly appears in the urine, but nevertheless candida renal infections may respond to intravenous miconazole.[7] Metabolic breakdown occurs in the liver, various metabolites being excreted in bile and urine. Metabolism and excretion seem little influenced by renal insufficiency.

As yet no data are available about toxicity of miconazole in premature infants, but toxicity in adults has been largely associated with the carrier solution, Cremophor EL. Reported effects include microcytic anaemia, thrombocytosis, and increased serum triglycerides; all these are reversed after stopping treatment.[8]

Little is known about blood levels of miconazole in babies, and there is as yet no agreement about the most suitable dosage regimen. In Case 2, an intravenous dose of 4 mg/kg daily resulted in apparent elimination of *Candida* sp. from sputum and urine, and the recurrence may have been due to the fact that the central venous cannula was left *in situ*. The plasma miconazole levels showed no evidence of drug accumulation in the blood over 7 days, at the higher dose of 7·4 mg/kg twice daily, despite the fact that the baby was very ill, and this dose was clinically effective.

With the increasing use of parenteral alimentation in the management of premature infants, systemic candidiasis is likely to become more common. Early diagnosis is essential, and the finding of hyphae in the urine is important in this context. None of the drugs previously used in this condition is entirely satisfactory. This is probably also true of miconazole; and information about its effects in premature infants is still scanty. Nevertheless, miconazole may prove a useful addition to the treatment available for this dangerous disease.

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