Trimethoprim sulphamethoxazole in neonatal *Flavobacterium meningosepticum* infection

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**SUMMARY** During an outbreak of *Flavobacterium meningosepticum* septicaemia in a neonatal intensive care unit 9 infants were treated with intravenous trimethoprim sulphamethoxazole. Bacteriological cure was achieved in 8 patients; one infant died of massive intraventricular haemorrhage on the first day of treatment. Apart from prolonged persistence of pre-existing thrombocytopenia there was no evidence of side effects. Trimethoprim sulphamethoxazole should be considered in the treatment of neonatal *F meningosepticum* sepsis in view of its activity against this organism, good penetration of the blood brain barrier, and the absence of serious side effects.

*Flavobacterium meningosepticum*, an opportunistic Gram negative bacillus, has been implicated in several outbreaks of epidemic meningitis and septicaemia in newborn nurseries causing appreciable morbidity and mortality.\(^3\) It is characteristically resistant to conventional first line treatment for neonatal sepsis including penicillin, ampicillin, chloramphenicol, kanamycin, and gentamicin. It is generally susceptible to erythromycin, vancomycin, rifamycin, clindamycin, and trimethoprim sulphamethoxazole. The use of this combination antibiotic in neonatal *F meningosepticum* sepsis has not been described previously.

**Patients and methods**

**Patients.** In January 1982 *F meningosepticum* was isolated from blood cultures of 9 newborn infants within a 6 day period in the neonatal intensive care unit at the Hadassah University Hospital. Clinical data on the patients are presented in the Table.

**Bacteriological procedures.** Cultures and identification were performed according to Rubin et al.\(^4\) Susceptibility testing was performed as described by Barry and Thornsberry.\(^4\)

**Laboratory monitoring.** Haemoglobin, white cell count, platelets, acidbase, electrolytes, bilirubin, urea, and urinalysis were checked at least daily. Urine microscopy was performed on alternate days. Blood cultures were drawn before and two to three days after starting treatment with trimethoprim sulphamethoxazole. Lumbar puncture was performed on five of the 9 patients before treatment.

**Results**

**Clinical manifestations.** Signs of neonatal sepsis included lethargy, bradycardia, apnoea, acidosis, and bleeding tendency. Abdominal distension was an early indicator of sepsis in all 9 infants. In three patients considerable intra-abdominal pathology, necrotizing enterocolitis, ileal perforation, and postoperative duodenal atresia preceded the onset of the septicaemia. All infants were receiving hyperalimentation at the time of their illness and none had received enteral nutrition.

**Bacteriological studies.** The antibiotic susceptibility pattern of *F meningosepticum* isolated from all 9 infants was identical: the organism was sensitive to tetracycline, fuxitin, and trimethoprim sulphamethoxazole; was resistant to ampicillin, cephalozin, amikacin, and gentamicin; and had an intermediate sensitivity to chloramphenicol and erythromycin. Blood cultures taken from the 8 surviving patients two to three days after starting treatment were sterile. Cerebrospinal fluid samples obtained from five patients before treatment were sterile.
Treatment protocol. The first three patients were treated initially with ampicillin and amikacin. When the identity and sensitivities of the infecting organism were realised treatment was changed to trimethoprim sulphonmethoxazole and all subsequent patients were treated from the onset with this. A solution containing trimethoprim (16 mg/ml) and sulphonmethoxazole (80 mg/ml) was diluted to 1:20 in 5% dextrose in water and was given intravenously over 10 minutes. The dosage schedule was trimethoprim (2.5 mg/kg/day) and sulphonmethoxazole (12.5 mg/kg/day) divided into two equal doses, and given over a period of 10 days.

Outcome. One of the infants (case 5, Table) died within 24 hours of beginning antibiotic treatment; a massive intraventricular haemorrhage (grade 4) had been found previously in this patient. The remaining 8 infants all recovered clinically and bacteriologically from the \textit{F meningosepticum} sepsis. Of the 8 initial survivors, however, two subsequently died—the infant in case 4 as a result of hydrocephalus secondary to intraventricular haemorrhage and case 7 from hepatic failure secondary to prolonged hyperalimentation three months after the flavobacterium sepsis. A third infant, case 6, has moderately severe psychomotor retardation secondary to severe birth asphyxia.

Complications of treatment. No cutaneous or gastrointestinal side effects were observed. There was no indication of nephrotoxicity as judged by blood urea and urine output and no evidence of sludging of the drug was found on urine microscopy. Haemoglobin concentrations and white cell count were not affected by trimethoprim sulphonmethoxazole. All 9 patients had thrombocytopenia (12 000–50 000/mm$^3$), which was present before treatment began but persisted for up to 34 days from the beginning of the sepsis.

Discussion

\textit{F meningosepticum} has a propensity for causing sepsis in newborns and a predilection for preterm infants. The particularly poor prognosis may be attributed in part to delay in establishing the identity of the organism and its unusual antibiotic sensitivity which renders it insensitive to the standard first line treatment for neonatal sepsis.

Recommended treatment has included vancomycin, erythromycin, and rifamycin. Erythromycin given parenterally does not achieve adequate concentrations in the cerebrospinal fluid and therefore needs to be given intravenicularly in meningitis. The development of resistance to both erythromycin and vancomycin during treatment has been described. Rifamycin does not cross the blood brain barrier and, in addition, conjugated hyperbilirubinaemia was associated with its use in two out of three patients. We chose trimethoprim sulphonmethoxazole because of the proved sensitivity of the organism to this combination antibiotic, its ability to cross the blood brain barrier, and our previous favourable experience with it in neonates.$^5$

Meningitis is a common event in neonatal \textit{F meningosepticum} sepsis. Progression of septicaemia

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Gestation (weeks)</th>
<th>Birthweight (g)</th>
<th>Age at onset (days)</th>
<th>Complicating factors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>30</td>
<td>1100</td>
<td>9</td>
<td>Patellar dactylus, ileal perforation</td>
<td>Ileostomy closed at 5 months. Now healthy</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>28</td>
<td>805</td>
<td>12</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>35</td>
<td>1600</td>
<td>31</td>
<td>Tracheo-oesophageal fistula, duodenal atresia</td>
<td>Feeding jejunostomy; recurrent pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>27</td>
<td>960</td>
<td>10</td>
<td>Hyaline membrane disease, intraventricular haemorrhage, patent dactylus arteriosus</td>
<td>Died aged 28 days from hydrocephalus</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>27</td>
<td>860</td>
<td>10</td>
<td>Hyaline membrane disease, intraventricular haemorrhage, patent dactylus arteriosus</td>
<td>Died aged 11 days from massive intraventricular haemorrhage</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>36</td>
<td>2680</td>
<td>3</td>
<td>Hyperbilirubinaemia (after exchange transfusion)</td>
<td>Neurological damage</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>28</td>
<td>835</td>
<td>10</td>
<td>Necrotizing enterocolitis</td>
<td>Died aged 3 months from liver failure</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>28</td>
<td>940</td>
<td>28</td>
<td>Hyaline membrane disease, patent dactylus arteriosus (surgically closed)</td>
<td>Healthy</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>33</td>
<td>1305</td>
<td>20</td>
<td>Hyaline membrane disease, patent dactylus arteriosus (surgically closed)</td>
<td>Healthy</td>
</tr>
</tbody>
</table>
to meningitis before beginning appropriate treatment has been documented and perhaps early treatment with trimethoprim sulphanethoxazole prevented this sequence of events in our patients.

Would trimethoprim sulphanethoxazole have been suitable treatment if meningitis had occurred? Sabel and Brandberg showed excellent results with trimethoprim sulphanethoxazole in neonates and infants with either meningitis or septicaemia, or both, who were considered to be treatment failures after conventional antibiotic treatment. High concentrations of the drug were achieved in the cerebrospinal fluid with parenteral administration.

Concern has been expressed over the use of trimethoprim sulphanethoxazole in the neonatal period because of potential side effects, particularly haematological abnormalities and kernicterus due to displacement of bilirubin from albumin by the sulphonamide component. The finding of thrombocytopenia in all our patients preceded treatment but thrombocytopenia persisted (without bleeding tendency) for up to 34 days. This may be attributed to either flavobacterium sepsis or trimethoprim sulphanethoxazole, or both. No other haematological abnormalities were noted. We have already shown in vitro that sulphanethoxazole does not displace bilirubin from albumin binding sites even in concentrations well above the therapeutic range.

References

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