Rifampicin in pneumococcal meningoencephalitis

M J Peters, B L Pizer, M Millar

Abstract
The cases are reported of two infants with pneumococcal meningitis in whom initial antibiotic treatment was ineffective despite the organisms being sensitive to the drugs used. A clinical and radiological diagnosis of meningoencephalitis was made. A rapid improvement followed the addition of rifampicin treatment.

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Pneumococcal meningitis is a life threatening disease with an incidence of 1–3 in 100 000. Mortality may be as high as 30%. A large proportion of survivors have significant neurological impairment. Pneumococcal meningitis is often treated with β lactam antibiotics such as penicillin or cefotaxime. Among the many serious complications of pneumococcal meningitis is direct bacterial invasion of brain tissue, termed 'meningoencephalitis' or 'cerebritis'. This may present as persistent drowsiness, coma, confusion, convulsions, and focal neurological signs. In severe cases characteristic features may be seen by computed tomography. These findings have a significant association with persistent abnormal neurological signs and particularly subsequent epilepsy.

Rifampicin has its major use in the treatment of tuberculosis infection, including tuberculous meningitis, and has a wide spectrum of activity against Gram positive organisms. Rifampicin is highly lipid soluble and penetrates cell membranes well, achieving high concentrations of cerebrospinal fluid, even in the absence of inflamed meninges. As a result it has been recommended for use in staphylococcal or listerial central nervous system infection or in cases of an infected ventriculoperitoneal shunt, in which there may be little or no meningeal inflammation. Rifampicin has also been used in combination treatment for meningitis caused by brucella and flavobacterium species.

We report the cases of two infants with proved pneumococcal meningitis with organisms shown to be sensitive to β lactam antibiotics and in whom clinical and radiological evidence of severe meningoencephalitis did not resolve while receiving β lactam antibiotic treatment. In both infants the addition of rifampicin was followed by a striking clinical improvement.

Case reports
CASE 1
A previously well 4 week old male infant was admitted with a 24 hour history of poor feeding, vomiting, and irritability. He had not received antibiotic treatment before admission. On examination he was pyrexial (38-2°C) and irritable.

Initial investigations were as follows: haemoglobin 115 g/l, white cell count 6.0×10⁹/l (neutrophils 3-3), and platelets 440×10⁹/l. Plasma electrolytes were normal. Microscopy of lumbar cerebrospinal fluid showed white cell count 960×10⁹/l, red cell count 415×10⁹/l, and numerous Gram positive cocci. He was treated with intravenous cefotaxime (200 mg/kg/day), netilmicin (7-5 mg/kg/day), and dexamethasone (0-15 mg/kg every six hours for four days).

Culture of cerebrospinal fluid confirmed a pure growth of Streptococcus pneumoniae sensitive to cefotaxime by disc susceptibility testing. The infant remained pyrexial and irritable. Forty eight hours after admission he had several episodes of hypotonia and decreased responsiveness. Repeat electrolyte and calcium measurements were normal. An electroencephalogram confirmed widespread epileptic activity. Computed tomography of his brain showed ventriculitis and encephalitis, but no evidence of raised intracranial pressure. The convulsions were difficult to control, only partially responding to intravenous phenobarbitone and an infusion of paraldehyde.

Eight days after admission he remained pyrexial (38-7°C) (fig 1) and irritable on...
handling, with occasional convulsive movements. Repeat lumbar puncture showed persistent cerebrospinal fluid neutrophilia but no organisms on Gram staining and no growth on culture. Repeat computed tomography showed persisting ventriculitis and cerebritis.

In view of the unsatisfactory response to treatment, rifampicin (20 mg/kg/day, given in two divided doses) was added intravenously on the 13th day after admission. The next day a dramatic clinical improvement was noted with decreased convulsions, improved feeding, and a more normal cry. His temperature settled to normal within 36 hours for the first time since admission (Fig 1). He continued to improve while receiving intravenous rifampicin for nine days, followed by rifampicin by mouth for eight days. On discharge on day 27 he was smiling, fixing, following with his eyes, and moving his limbs appropriately, except for decreased use of his right arm.

CASE 2
A previously healthy 8 month old infant was admitted after a prolonged generalised convulsion. He had been irritable, sleepy, and vomiting intermittently for 48 hours before the convulsion. He was pyrexial (38.6°C) with generalised poor tone but no focal neurological deficits. He continued to have fits despite rectal diazepam and intravenous phenytoin (10 mg/kg), but his seizures were eventually controlled with a paraldehyde infusion.

Cerebrospinal fluid examination showed a white cell count of 260×10⁶/l (90% neutrophils) and numerous Gram positive cocci later confirmed as pneumococci sensitive to benzylpenicillin, cefotaxime, and chloramphenicol on disc susceptibility testing. He was treated with benzylpenicillin (200 mg/kg/day), chloramphenicol (100 mg/kg/day), and dexamethasone (0-2 mg/kg every six hours for five doses). His condition stabilised and penicillin was stopped after 36 hours. On day four of this admission he had a number of generalised and left sided focal seizures. Computed tomography showed meningoencephalitis and a small infarct in the right internal capsule. Antibiotic treatment was changed to intravenous cefotaxime alone (200 mg/kg/day). His clinical status remained poor with continuing fever, irritability, and occasional fits despite phenytoin and phenobarbitone.

On day 12 cefotaxime was discontinued. Twenty four hours later he deteriorated with a recurrence of high fever and increased fits. Repeat computed tomography confirmed persistent cerebritis (Fig 2). Cefotaxime was restarted with the addition of intravenous rifampicin (20 mg/kg/day in two divided doses). He made a rapid recovery with his temperature falling to normal within 36 hours and a complete cessation of his fits (Fig 1). He was maintained on intravenous antibiotics for a further three weeks before taking rifampicin and co-trimoxazole by mouth for two weeks.

On discharge he had marked left hemiparesis and a mild right sided weakness. Repeat computed tomography showed generalised cerebral atrophy with resolution of the appearances of cerebritis.

Discussion
These cases show a clear clinical improvement in severe pneumococcal meningoencephalitis with rifampicin treatment. This followed the failure of a prolonged course of treatment with antibiotics to which the pneumococcal isolates were sensitive. A previous report of pneumococcal meningitis in the presence of a venticuloperitoneal shunt describes similar findings. Rifampicin with benzylpenicillin and cefotaxime for nine days was ineffective, but after the addition of rifampicin the child made a rapid recovery without removal of the shunt.

We believe our patients are not typical in that the degree of cerebritis was much greater than the characteristically mild disorder seen in many cases of bacterial meningitis. This fact may partially explain the dramatic response achieved with rifampicin because of the high cerebrospinal fluid levels and excellent tissue penetration it exhibits, even in the absence of marked meningeval inflammation. Another possible explanation for the efficacy of rifampicin may have been the persistence of bacteria within host cells which provide an effective barrier to β lactam antibiotic treatment. In this situation the intracellular penetration of rifampicin may have allowed it to be effective in eradicating infection when treatment with antibiotics with poor cell penetration had failed. Lastly, bacterial exposure to β lactam antibiotics may result in the formation of cell wall deficient bacteria or 1 forms. Rifampicin is effective against cell
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wall deficient bacteria and may have eradicated cell wall deficient pneumococci in these two patients.

We conclude that in pneumococcal meningitis when β-lactam antibiotics are ineffective, the diagnosis of meningoencephalitis should be considered. In this situation rifampicin may be a useful addition to the treatment.

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