Piperacillin in early neonatal infection

M PLACZEK, A WHITELAW, S WANT, M SAHATHEVAN, AND J DARRELL

Department of Paediatrics and Neonatal Medicine and Department of Bacteriology,
Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY Seventy infants with suspected bacterial infection in the first 48 hours of life were treated either with piperacillin and flucloxacillin or with penicillin and gentamicin. Infection was confirmed and successfully eradicated in 6 of the 35 infants receiving piperacillin and flucloxacillin. Four infants treated with penicillin and gentamicin had confirmed infection and one deteriorated initially but then recovered when treated with piperacillin. Serum piperacillin concentrations above 100 mg/l and cerebrospinal fluid piperacillin concentrations of 2.6-6 mg/l were noted for up to four hours and 7 hours respectively, even in the absence of inflamed meninges, after administration of piperacillin 100 mg/kg body weight intravenously. Median half life of piperacillin was 6.5 hours and was prolonged in renal impairment. Piperacillin is considered to be a safe and effective first line single agent treatment for early neonatal infection but because some *Escherichia coli* are resistant to it we recommend that a second agent be used in critically ill infants with neutropenia or meningitis.

In spite of recent advances in neonatal intensive care early septicaemia in the first 48 hours of life carries a high risk of mortality.¹⁻³ The combination of penicillin and gentamicin has become well established as initial treatment, but there is concern about the ototoxicity of gentamicin, particularly in the presence of renal failure.⁴⁻⁶ To avoid toxicity and because of delays in assaying gentamicin this antibiotic is sometimes prescribed in inadequate doses. Another disadvantage of gentamicin is its poor penetration into cerebrospinal fluid (CSF).⁷

We considered piperacillin, a new semi-synthetic ureidopenicillin, as a possible alternative because it is effective against likely perinatal pathogens—namely, group B streptococcus, *Escherichia coli*, pneumococcus, *Haemophilus influenzae*, klebsiella, pseudomonas, and *Listeria monocytogenes*⁸⁻¹⁰—and because it has not shown serious toxicity when used previously in adults and children.^{11 12} Piperacillin, with and without gentamicin, has been used successfully in neonatal infections in one uncontrolled study.¹³ Our study compares the efficacy of piperacillin and flucloxacillin with penicillin and gentamicin in the management of early neonatal infection as assessed by clinical recovery, bacteriological cure, incidence of resistant organisms, subsequent emergence of resistant organisms, serum pharmacokinetics, and penetration of CSF. Flucloxacillin was added to the treatment because piperacillin is not active against staphylococci that produce penicillinase, and these organisms had previously been reported as early pathogens in our hospital.¹

Subjects and methods

For 8 months from July 1982 all infants in a regional neonatal intensive care unit who were suspected of having a bacterial infection in the first 48 hours of life were entered into a trial. There were 70 in all. The infants were allocated alternately into a study group who received piperacillin and flucloxacillin, and a control group who received penicillin and gentamicin. Doses of piperacillin (100 mg/kg) and flucloxacillin (25 mg/kg) or gentamicin (2.5 mg/kg) and penicillin (60 000 U/kg) were given intravenously every 12 hours. Piperacillin (200 mg/kg/12 hours) was given for meningitis. Antibiotics were continued for five to 16 days when infection was confirmed but discontinued after three to four days if clinical status and laboratory investigations did not confirm infection. Before starting treatment with antibiotics, bacterial cultures of superficial swabs, blood, and urine were made and, where indicated, endotracheal aspirates and CSF. All infants in the trial then had superficial swabs, urine, and stool cultures taken weekly until 6 weeks of age or until discharge, to detect the emergence of resistant organisms. After the third or fourth injection of piperacillin, serum was assayed for piperacillin using an agar diffusion technique¹⁴ with DST agar and *E. coli* NCTC 10418 as the assay organism. This

organism was totally resistant to flucloxacillin, which did not therefore interfere with the assay for piperacillin.

Results

The infants treated with piperacillin and flucloxacillin were similar to those treated with penicillin and gentamicin in birthweight (mean 1625 and 1665 g respectively), gestational age (mean 31.5 and 31.7 weeks respectively), incidence of membranes ruptured for more than 24 hours (46% and 49% respectively), incidence of maternal treatment with antibiotics (29% and 37% respectively), and age at start of treatment with antibiotics (mean 12.2 and 10.2 hours respectively).

Clinical evidence confirmed infection in 6 infants treated with piperacillin and flucloxacillin and in four treated with penicillin and gentamicin. Blood cultures were positive in one of the 6 and two out of the four respectively. Perinatal pathogens were isolated from other sites (Table 1). In all those receiving piperacillin and flucloxacillin the infection was eradicated. No serious side effects were apparent in either group of infants. The condition of one of the babies treated initially (case 35) with penicillin and gentamicin deteriorated and treatment was changed to piperacillin. There was no early staphylococcal infection.

Gram negative meningitis. One infant weighing 2120 g at 35 weeks' gestation (case 35) and with severe asphyxia at birth developed *E. coli* septicaemia and meningitis at 24 hours of age. Piperacillin

(200 mg/kg/12 hours) rendered the CSF sterile after 24 hours' treatment. A single loading dose of amikacin (8 mg/kg intravenously) was subsequently given, but the infant died at age 7 days from renal failure and cerebral haemorrhagic infarction. Necropsy examination showed the meninges to be histologically normal, and cultures were negative. An infant of 31 weeks' gestation and weighing 1680 g (case 36) developed pseudomonas septicaemia and meningitis within 24 hours of birth. Initial treatment was with penicillin and gentamicin, but the infant's condition deteriorated, and, when the organism was shown to be Gram negative, piperacillin (200 mg/kg/12 hours) was started. Treatment with intravenous amikacin (10 mg/kg/24 hours) was added after a further 24 hours. The infant rapidly improved; the CSF was sterile after four days' treatment. She recovered completely and was developmentally normal aged 6 months. In this infant the CSF piperacillin concentration was 190 mg/l two and a half hours after an intravenous injection of 200 mg/kg. In a group of infants without meningitis, CSF piperacillin concentrations of 2.6–6 mg/l were found up to 7 hours after administration of 100 mg/kg intravenously (Table 2). These concentrations are bactericidal for all group B streptococci and 79% of enteric Gram negative bacilli.¹⁵

Emergence of organisms resistant to piperacillin. Although all the bacteria responsible for early infections were fully sensitive to piperacillin, in four infants treated with piperacillin and flucloxacillin and in 7

Table 1 Infants with confirmed early infection

Case No	Gestation (weeks)	Birthweight (g)	Clinical evidence of infection	Bacteriology	Antibiotic treatment	Outcome
21	28	1250	Hypotension, sclerema	<i>S pneumoniae</i> (rectum)	Piperacillin and flucloxacillin	Recovered
35	35	2120	Hypotension, sclerema, disseminated intravascular coagulation	<i>E coli</i> (blood and CSF)	Piperacillin and flucloxacillin with amikacin	Blood & CSF sterilised. Death at 8 days from consequences of birth asphyxia
9	33	1840	Pneumonia	<i>E coli</i> (throat and nose)	Piperacillin and flucloxacillin	Recovered
25	31	1760	Pneumonia	Negative (maternal antibiotics)	Piperacillin and flucloxacillin	Recovered
39	27	900	Respiratory distress, neutrophilia, early jaundice	Negative (maternal antibiotics)	Piperacillin and flucloxacillin	Recovered
43	26	800	Respiratory distress, jaundice, acidosis	<i>E coli</i> (umbilicus)	Piperacillin and flucloxacillin	Recovered
10	38	2880	Hypotension, sclerema, DIC	<i>S pneumoniae</i> (blood)	Benzylpenicillin and gentamicin	Recovered
26	31	1680	Hypotension, acidosis	<i>Pseudomonas</i> (blood and CSF)	Benzylpenicillin and gentamicin, then piperacillin and amikacin	Recovered after initial deterioration
2	31	1110	Respiratory distress neutrophilia	<i>E coli</i> (throat)	Benzylpenicillin and gentamicin	Recovered
44	26	940	Pneumonia	Negative (maternal antibiotics)	Benzylpenicillin and gentamicin	Recovered

Table 2 Cerebrospinal fluid concentrations of piperacillin in infants receiving 100 mg/kg/12 hours

Case No	Time after piperacillin injection (hours)	No of doses after start of treatment	CSF piperacillin concentration (mg/l)	Blood piperacillin concentration (mg/l)	
				1 hour	12 hours
34	6	6	2.6		
39	7	1	6	130	50
44	24	20	*		
57	12	1	6	140	65
N†	10	10	*	90	*
26	2.5‡	4	190	800	180
26	11	8	*	100	*

*Not detected.

†Infant becoming ill at 4 days old and therefore not included in trial.

‡Infant receiving 200 mg/kg/12 hours.

with penicillin and gentamicin superficial swabs indicated colonisation by Gram negative organisms moderately or completely resistant to piperacillin. In one such infant receiving piperacillin a moderately resistant *Enterobacter aerogenes* caused septicaemia in association with a central venous catheter. Only one infant subsequently became colonised with an organism resistant to gentamicin—namely, *Serratia marcescens*.

Pharmacokinetics. The median half life of piperacillin was 6½ hours (range 3.5–14). Piperacillin excretion was not influenced by gestational age or birthweight, and there was no evidence of drug accumulation over five days. There was a tendency for the most sick infants—namely, those with severe metabolic acidosis, renal impairment, and shock—to show slightly slower elimination of piperacillin (Figure).

Figure Mean (SEM) serum concentrations of piperacillin after intravenous injection of 100 mg/kg in three neonates with shock and impaired renal function (plasma urea concentration over 12 mmol/l (72 mg/100 ml) (▲), 8 neonates with plasma urea concentrations 6.5–12 mmol/l (39–72 mg/100 ml) (○), and 9 neonates with plasma urea concentrations below 6.5 mmol/l (39 mg/100 ml) (◆).

Piperacillin assays on serum before and after exchange transfusion and on the waste blood from the exchange showed that all the piperacillin was removed by a two volume exchange transfusion.

Discussion

Piperacillin and flucloxacillin were successful in eradicating organisms in the infants with proved early infection. Within the group treated with penicillin and gentamicin the condition of one infant with pseudomonas meningitis deteriorated and treatment had to be changed. None of the 70 infants studied had a pathogen in the first 48 hours that was resistant to piperacillin. Because of the absence of staphylococci in early neonatal infection during the last three years at our hospital⁹ we no longer consider flucloxacillin to be essential in initial treatment.

The emergence of partially resistant organisms after treatment with piperacillin may be related to the considerable excretion of piperacillin via the biliary tract into the gut,¹⁶ where resistant strains are selected. We recommend that in nurseries where piperacillin is used for treatment of early infection an alternative antibiotic, to which the bacteria have not been exposed, should be used for treatment of later infections.

Serum concentrations of over 100 mg/l were consistently obtained for at least four hours after injection of 100 mg/kg intravenously. Piperacillin concentrations of 10 mg/l will successfully inhibit all group B streptococci and pneumococci, 90% of *Haemophilus influenzae*, *serratia* and *pseudomonas*, and 75% of isolates of *E. coli*.^{9,10} For most organisms there is little or no difference between bactericidal and bacteriostatic concentrations.⁸ The serum half life of piperacillin is prolonged in children with renal impairment.¹⁷ This was confirmed in our own study in the few infants with shock, acidosis, and raised blood urea concentrations, but the clearance was not otherwise influenced by gestational age, birthweight, or diuretic treatment. Thus 100 mg/kg/12 hours can be given routinely in neonates. Exchange transfusion has been advocated in the management of septicaemia with sclerema.¹⁸ After exchange transfusion a full dose of piperacillin should be given to replace that removed in the waste blood.

The choice of antibiotic treatment for neonatal Gram negative meningitis has been unsatisfactory in the past because of poor penetration of aminoglycosides into the CSF⁷ and because of the toxicity of chloramphenicol.¹⁹ Hoogkamp-Korstanje successfully treated three preterm infants with Gram negative meningitis with piperacillin and gentamicin.¹³ We found very good CSF penetration in meningitis, and, even without meningeal inflamma-

tion, piperacillin was detectable up to 7 hours after injection at concentrations bactericidal for most likely pathogens.

Because of the difficulties in diagnosing early neonatal infection combined with the fatal outcome if not promptly treated, a high proportion of sick infants admitted to neonatal intensive care units will receive broad spectrum antibiotic treatment, though subsequent results may confirm infection in only a minority. It is therefore essential that the antibiotics should be not only effective against the prevalent perinatal pathogens but should be safe, free from toxic side effects, and have a simple dose regimen. From our experience, piperacillin fulfills these requirements and promises to be a suitable first line single agent treatment for suspected early neonatal infection. In life threatening infection, use as sole treatment would be unwise because of the resistance to piperacillin of some *E. coli*.⁸⁻¹⁰

After the end of the period of study we encountered four infants with early onset Gram negative septicaemia (one with meningitis). Two of the organisms were fully sensitive to piperacillin and two were moderately resistant. Meningitis developed while the infant was being treated with penicillin and gentamicin. In critically ill infants with severe neutropenia, and in neonatal meningitis, we recommend that piperacillin be used in conjunction with a second drug such as an aminoglycoside or a third generation cephalosporin.

We thank Lederle Laboratories for a project grant.

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Correspondence to Dr Monica Placzek, Ryegate Annexe, Tapton Crescent Road, Sheffield S10 5DD.

Received 9 September 1983