

Experiences with carbenicillin in the treatment of septicaemia and meningitis

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Summary

Experiences in the use of carbenicillin, a new penicillin active against *Pseudomonas aeruginosa* and other Gram-negative bacteria in the treatment of septicaemia and meningitis are described. Blood levels of carbenicillin in excess of the levels required to inhibit the infecting organisms were obtained using intravenous infusions of large doses together with probenecid by mouth. High cerebrospinal fluid levels of carbenicillin were ensured in the meningitis patients with daily intrathecal or intraventricular injections. Carbenicillin undoubtedly controlled the course of *Ps. aeruginosa* septicaemia in two patients.

Rapid sterilization of the cerebrospinal fluid was achieved in both meningitis patients with clinical improvement.

No evidence of toxicity was seen and daily intrathecal injections were well tolerated.

Introduction

Carbenicillin (BRL 2064, Pyopen†)—disodium α -carboxybenzyl penicillin—is a new semi-synthetic penicillin having a wide spectrum of antibacterial activity. It is not absorbed following oral administration and must therefore be given by injection (Acred *et al.*, 1967). Animal studies have shown carbenicillin to be virtually non-toxic. Knudsen, Rolinson & Sutherland (1967).

Carbenicillin is active against Gram-negative organisms including *Escherichia coli*, and *Proteus* strains. Its main interest, however, lies in its activ-

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‡Pyopen is the registered trade name for carbenicillin produced by Beecham Research Laboratories England and Beecham Products Inc. U.S.A.

ity against strains of *Pseudomonas aeruginosa* and those strains of *Proteus* normally resistant to ampicillin, for example, *Proteus rettgeri*, *Proteus morgani* and *Proteus vulgaris*. Carbenicillin also has some Gram-positive activity although considerably less than that possessed by ampicillin or penicillin G and is not active against penicillinase-producing staphylococci, since it is destroyed by staphylococcal penicillinase.

Strains of *Pseudomonas aeruginosa* are sensitive to 12.5-250 $\mu\text{g/ml}$ of carbenicillin, the majority being sensitive to 50 $\mu\text{g/ml}$ (Knudsen *et al.*, 1967). Although this degree of activity is considerably less than that generally accepted for a useful systemically administered antibiotic the high urinary concentrations of carbenicillin obtainable following intramuscular dosage have enabled *Pseudomonas aeruginosa* infections of the urinary tract to be treated successfully (Brumfitt, Percival & Leigh, 1967).

The successful treatment of severe systemic infections such as septicaemia and meningitis, however, depends on the attainment and maintenance of blood levels at least as high as the minimum inhibitory concentration. In the case of *Pseudomonas aeruginosa* strains, therefore, blood levels in the region of 100 $\mu\text{g/ml}$ are required. Transient levels of this order may be achieved following 1-g intravenous doses of carbenicillin (Knudsen *et al.*, 1967), but the maintenance of such a level requires either repeated intravenous injections or continuous infusion. The low toxicity of carbenicillin enables large doses to be given with safety and if probenecid is given by mouth in addition-sustained blood levels sufficiently high to inhibit strains of *Pseudomonas aeruginosa* and other Gram-negative organisms may be achieved (Robinson & Sutherland, 1967).

Carbenicillin, like other penicillins does not

pass readily into the cerebrospinal fluid (CSF) and the successful treatment of meningitis will, in view of the high concentrations required to inhibit *Pseudomonas aeruginosa* strains, require local injection into the cerebrospinal fluid in addition to systemic therapy.

This paper describes our experiences with carbenicillin in septicaemia and meningitis. *Pseudomonas* septicaemia was confirmed in one patient and strongly suspected in another, whilst in the meningitis patients the infecting organism was *Pseudomonas aeruginosa* in one and a paracolon organism in the other.

Case 1

An 18-year-old man previously treated for Hodgkin's disease relapsed and was admitted to the Royal Marsden Hospital with splenomegaly and fever. In spite of intensive therapy with cytotoxic drugs and steroids he deteriorated and became jaundiced. He developed severe marrow depletion and required intensive platelet infusion support. *Pseudomonas aeruginosa* was isolated from his throat, nose, hands and urine and subsequently he developed numerous skin lesions which were considered to be septic emboli from a *Pseudomonas aeruginosa* septicaemia since a blood culture showed the presence of this organism. He was given carbenicillin 24 g daily by intravenous infusion and probenecid 1 g 8-hourly by mouth, following which there was a temporary improvement, but 9 days after the patient's blood culture was obtained he died as a result of the development of terminal oedema and ascites associated with right lower lobe pneumonia. A blood-culture taken prior to death grew *Esch. coli* and *Klebsiella pneumoniae*.

Case 2

A 35-year-old man admitted to the Royal Marsden Hospital with acute stem-cell leukaemia was treated with cytotoxic drugs and steroids and eventually went into remission. Subsequently he became pyrexial following a catheterization for acute retention at a time when *Pseudomonas aeruginosa* was repeatedly being isolated from his stools and throat as well as from dermatitis of the perineum. He transiently improved with intramuscular colistin, 4 mega-units daily, but his pyrexia increased and he became hypotensive. Although his blood culture at this time was sterile he was assumed to have *Pseudomonas aeruginosa* septicaemia and a further course of colistin with steroids was given. Since he continued to deteriorate colistin was discontinued and he was treated with 24 g carbenicillin daily by intravenous infusion increasing to 30 g daily. Probenecid 1 g 8-hourly by mouth was given

concurrently. Over a period of days the patient improved and became afebrile, and carbenicillin was discontinued after 2 weeks. At this stage he developed clinical signs of broncho-pneumonia for which he was given a 5-day course of chloramphenicol. This resolved and he was discharged. Subsequently he was readmitted 4 weeks later with a *Pseudomonas aeruginosa* urinary infection which responded to intramuscular colistin 4 mega-units daily. The strain of *Pseudomonas aeruginosa* isolated had unchanged sensitivity to carbenicillin.

Case 3

A 50-year-old woman was admitted unconscious to St George's Hospital Neurosurgical Unit with a 5-week history of frontal sinusitis and recent incision of a left frontal swelling, and was found after investigation to have a left subdural abscess. This was drained through frontal and temporal burr-holes. No organisms were grown from the pus obtained from the abscess although Gram-positive cocci were observed in the smear and it was felt advisable to administer cloxacillin, chloramphenicol and steroids systemically and subdurally. The patient improved temporarily but subsequently developed a swinging fever and her general condition deteriorated. Cerebrospinal fluid culture at this time grew *Pseudomonas aeruginosa*. Carbenicillin was given intravenously starting with a dosage of 6 g daily and increasing to 20 g daily together with probenecid orally, 1 g twice daily. Carbenicillin 40 mg daily was also given by intraventricular and intrathecal routes.

There was an immediate improvement following this therapy with fall in pyrexia, sterilization of CSF and fall in white cell count. On discontinuation of treatment the patient continued to improve although she was left with a residual neurological defect.

Case 4

A 19-year-old girl admitted to St George's Hospital Neurosurgical Unit with symptoms of an intracranial space-occupying lesion was found on investigation to have a retrosellar solid tumour. Following craniotomy and ventricular drainage a deterioration in the patient's condition was apparent and a paracolon organism was isolated from the CSF. There was no response to treatment with high intravenous dosage of ampicillin together with intrathecal ampicillin and steroids, cultures from the CSF remaining positive. Bacteriological sensitivity tests showed that the organism was considerably more sensitive to carbenicillin than to ampicillin. Carbenicillin was therefore given in a dose of 24 g daily

by intravenous infusion together with 50 mg 8-hourly intraventricularly. Probenecid 1 g 8-hourly was given also by mouth. The infection was rapidly controlled, the CSF becoming sterile in 3 days with fall in cell count. The patient subsequently collapsed and died. Necropsy findings revealed a sterile cerebrospinal fluid and a third ventricular malignant glioma growing into the hypothalamus and left temporal lobe.

Laboratory investigations

Venous blood samples were taken at intervals together with aliquots of several 24-hr urine collections on different days whilst patients were having carbenicillin treatment. Cerebrospinal fluid samples were taken before the next dose of carbenicillin was due in Cases 3 and 4. The separated serum, urine and CSF samples were immediately stored at -10°C to await assay at Beecham Research Laboratories.

The minimum inhibitory concentration (MIC) of carbenicillin was determined by conventional tube dilution technique using a 1 : 100 dilution of an overnight culture of the infecting organism. Serum, urine and CSF concentrations were determined using a conventional agar diffusion assay technique employing a highly sensitive strain of *Pseudomonas aeruginosa* as assay organism. The summarized results of these investigations are shown in Table 1. Blood counts and liver function tests were repeated during and after the course of carbenicillin treatment.

Results and discussion

The onset of *Pseudomonas aeruginosa* septicaemia is almost invariably a fatal complication of any illness since by the time the organism is identified an overwhelming infection is present. In order that treatment may stand a chance of

being effective antibiotic therapy must be instituted on a presumptive diagnosis. Frei *et al.* (1965) showed that the median survival time from the first positive blood-culture was only 2 days and that only two patients out of twenty-three lived more than 7 days after the first positive blood culture had been obtained.

Case 1 in this study in fact survived 9 days after his first positive blood-culture and his temporary clinical improvement could only be attributed to carbenicillin before he developed terminal *Esch. coli* and *Klebsiella pneumoniae* septicaemia.

Case 2 almost certainly had *Ps. aeruginosa* septicaemia and had progressively deteriorated in spite of hydrocortisone and colistin therapy. The administration of an intravenous carbenicillin infusion resulted in a gradual improvement in his condition and he was able to be discharged in remission following a short course of chloramphenicol for a clinical bronchopneumonia infection.

In both Cases 1 and 2 blood-levels considerably higher than those required to inhibit the strain of *Pseudomonas aeruginosa* (25 $\mu\text{g}/\text{ml}$) were consistently obtained. It is interesting that both these patients, however, continued to harbour the organism on the skin, throat or nose during treatment and that Case 2 subsequently developed a *Pseudomonas* infection of the urinary tract. There was, however, no suggestion of any decreased sensitivity to carbenicillin of the later isolates. Although no *Pseudomonas aeruginosa* could be isolated from blood culture during treatment from Case 1, superinfection occurred with *K. pneumoniae* which is invariably resistant to carbenicillin. The sensitivity of the *Esch. coli* strain isolated was not determined.

In both meningitis patients (Cases 3 and 4)

TABLE 1

Case	Age and sex	Diagnosis	Organism	MIC to carbenicillin ($\mu\text{g}/\text{ml}$)	Daily carbenicillin dose	Carbenicillin levels ($\mu\text{g}/\text{ml}$)		
						Serum	CSF	Urine
1	18 years, male	Septicaemia	<i>Ps. aeruginosa</i>	25	24 g i.v. daily (Probenecid 1 g 8-hourly)	63-250	—	—
2	35 years, male	Septicaemia?	<i>Ps. aeruginosa</i>	25	24-30 g i.v. daily (Probenecid 1 g 8-hourly)	140-400	—	9000
3	60 years, female	Meningitis	<i>Ps. aeruginosa</i>	125	6-20 g i.v. daily (Probenecid 1 g b.d.) 40 mg intrathecally + 40 mg intraventricularly daily	9-220	14-46 (24-hr levels)	9100- 31,000
4	19 years, female	Meningitis	Paracolon	2.5 MIC to ampicillin 50 $\mu\text{g}/\text{ml}$	24 g i.v. daily (Probenecid 1 g 8-hourly) 25 mg 8-hourly into left and right ventricle	17.5-125	Right ventricle 93-185 left ventricle 480 (8-hr levels)	5400- 15,700

there was, following carbenicillin treatment, a rapid return towards normality in the CSF findings, the results of which are shown in Fig. 1 and 2. The *Ps. aeruginosa* strain isolated from Case 3 was fairly resistant to carbenicillin having a MIC of 125 $\mu\text{g}/\text{ml}$ but serum levels in excess of this figure were frequently obtained. Since the 24-hr CSF levels in this patient varied from 14 to 46 $\mu\text{g}/\text{ml}$ levels prior to this must have been considerably higher. This patient's CSF culture became sterile after the first intrathecal and subdural administration of carbenicillin and remained so. Her CSF cell count dropped from 1000 to 10/ mm^3 after 6 days and her clinical state improved.

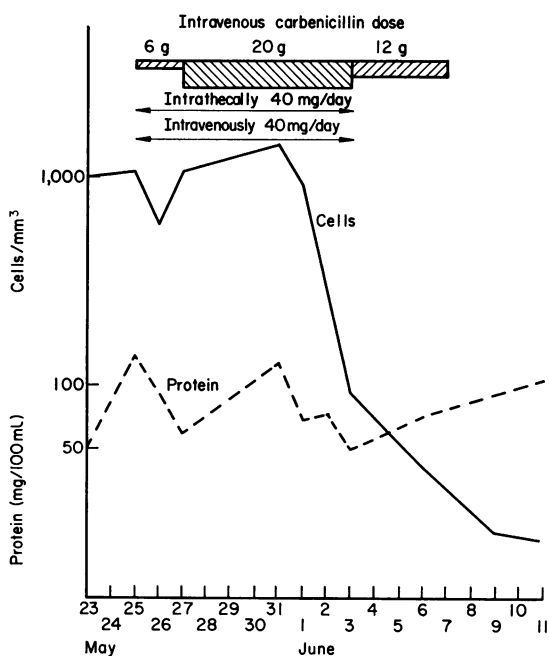


FIG. 1. Case 3.

Case 4 (Fig. 2) in spite of ampicillin therapy showed consistently positive CSF cultures, the paracolon organism having an MIC of 50 $\mu\text{g}/\text{ml}$ to ampicillin. In view of the greater sensitivity of the organism to carbenicillin (2.5 $\mu\text{g}/\text{ml}$) her treatment was changed to this penicillin and the CSF became sterile within 4 days; improvement of cell counts became normal within 2 weeks. Serum carbenicillin levels in this patient were consistently higher than the level required to inhibit the infecting organism and the particularly high levels obtained in the cerebrospinal fluid occasioned no signs of cerebral irritation.

Regular blood counts and liver function tests revealed no evidence of any toxic effect due to carbenicillin.

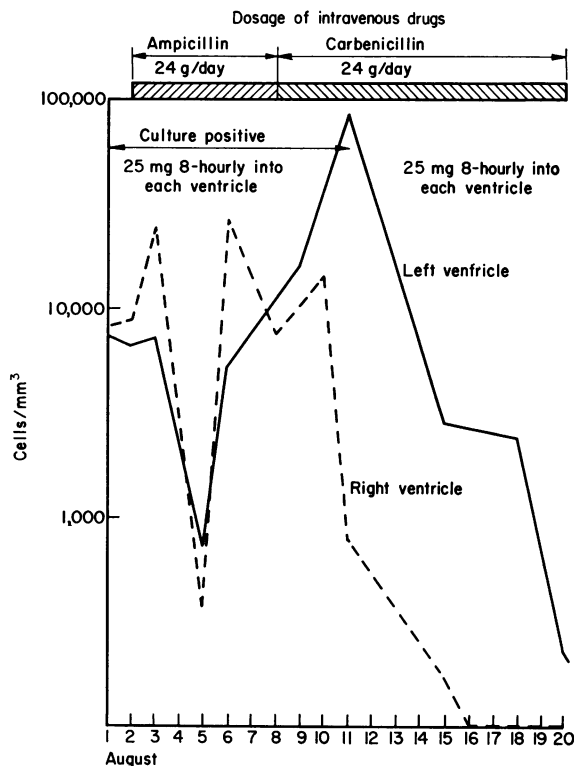


FIG. 2. Case 4.

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