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Ceftazidime compared with gentamicin and carbenicillin in patients with cystic fibrosis, pulmonary pseudomonas infection, and an exacerbation of respiratory symptoms

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ABSTRACT An open randomised comparison of a new intravenous cephalosporin, ceftazidime, with the established regimen of gentamicin and carbenicillin was carried out in patients with cystic fibrosis who had persisting pulmonary infection with *Pseudomonas* species and who developed acute exacerbations of respiratory symptoms. Fifty patients received ceftazidime and 32 gentamicin and carbenicillin. The ceftazidime and gentamicin were given every eight hours and the carbenicillin every six hours. The mean total daily doses were 151 mg/kg for ceftazidime, 6.3 mg/kg for gentamicin and 450 mg/kg for carbenicillin. The mean duration of treatment was 10 days in patients receiving gentamicin and carbenicillin and 12 days in those receiving ceftazidime. Of the patients with pseudomonas in the initial sputum specimen in whom sputum was cultured after treatment, six (26%) of 23 receiving gentamicin and carbenicillin and seven (18%) of 39 receiving ceftazidime had sputum free from pseudomonas at the end of treatment, but recolonisation occurred subsequently. In those receiving ceftazidime all 10 coexisting organisms were eliminated, whereas only four of seven coexisting organisms in patients receiving gentamicin and carbenicillin were eliminated. Overall clinical improvement occurred in 25 (78%) of 32 patients treated with gentamicin and carbenicillin and 48 (96%) of 50 patients treated with ceftazidime. Nineteen (59%) of the patients receiving gentamicin and carbenicillin but only 15 (30%) of those receiving ceftazidime required admission to hospital or intravenous antibiotics, or both, or died during the three months after treatment. Side effects in both groups were similar, mild, and infrequent. Thrombophlebitis occurred in four patients treated with gentamicin and carbenicillin but in no patients treated with ceftazidime.

Colonisation of the lungs with pseudomonas has become a major management problem in patients with cystic fibrosis, many of whom now survive to adolescence and adult life.[1] Patients thus affected are susceptible to recurrent exacerbations of respiratory symptoms. Treatment of these episodes with antibiotics to which the organism is sensitive may be followed by clinical improvement, but in only a minority of these patients are the organisms eliminated from the sputum by the end of treatment.[2] Invariably, the lungs are recolonised by pseudomonas within the next three months.[3] Failure to achieve permanent eradication of the organism has been attributed to incomplete penetration of antibiotics through pus and into the bronchial wall, their inhibition by cystic fibrosis sputum,[4] and the increased resistance of the mucoid forms of the organism that predominate in cystic fibrosis.

The standard regimens of treatment have previously consisted of a combination of a penicillin such as carbenicillin or azlocillin with an aminoglycoside such as gentamicin or tobramycin.[5,6] The penicillin is usually administered by intravenous infusion, and, as treatment is given for at least seven days, this is

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tedious for the patient and sometimes leads to thrombophlebitis. Over the two years from 1 January 1982 the British Thoracic Society Research Committee conducted a multicentre, open randomised trial of a new cephalosporin, ceftazidime. This has excellent in vitro activity against pseudomonas.[7 8] The results of this trial are reported here.

Patients and methods

Patients

Patients with cystic fibrosis who were over the age of 5 years and from whose sputum pseudomonas had been isolated on two occasions in the previous six months were eligible for the trial if they developed an acute exacerbation of respiratory symptoms. Patients could be admitted to the trial again on subsequent occasions provided they had not been taking antibiotics effective against pseudomonas within the previous two weeks. Pregnant women and patients allergic to penicillins, cephalosporins, or aminoglycosides were excluded as were patients with severe renal impairment. Drug resistance was not a criterion for exclusion, but clinicians were allowed to withdraw patients in whom pseudomonas was found to be resistant to particular drugs.

Written consent was obtained from patients aged 16 years and over and from the parents of patients under 16. The study was an open randomised trial. Treatment allocation was determined by drawing the next envelope of the batch supplied to each hospital, which contained randomly allocated treatment numbers.

Treatment regimens

The intravenous regimens for patients of 14 years and over were either carbenicillin 5 g every six hours by slow infusion over 30 minutes and gentamicin 80 mg every eight hours by bolus injection or ceftazidime 2 g every eight hours by bolus injection. Measurement of serum gentamicin concentrations was left to the discretion of clinicians, and the dose could be modified if the concentration was found to be outside the therapeutic range.

Children under 14 were given either carbenicillin 10 mg/kg every eight hours and gentamicin 2 mg/kg every eight hours or ceftazidime 40 mg/kg every eight hours. All drugs were to be given for a minimum of seven days.

Clinical assessment

Details of the patients' symptoms, abnormal physical signs, pulse rate, temperature, respiration rate, and sputum appearance and volume were recorded, and the degree of change in individual physical signs and symptoms was scored daily. Estimations of haemoglobin concentration, white blood cell count, and plasma urea and electrolyte concentrations were performed together with liver function tests before and after treatment and as required. Peak expiratory flow rate (PEFR) was recorded daily in 24 patients receiving ceftazidime and 21 receiving gentamicin and carbenicillin. Weight before and after treatment was recorded, and an overall assessment of each patient's condition before and after treatment was made by the clinician based on all available clinical and lung function data. Clinical assessment and lung function tests were repeated two to four weeks and three months after completion of the treatment.

At the end of the study patients were divided into those who had shown clinical improvement and those who had not on the basis of the change in individual symptoms and physical signs and on an overall assessment by the clinician in charge of the case of the response to treatment.

Bacteriological studies

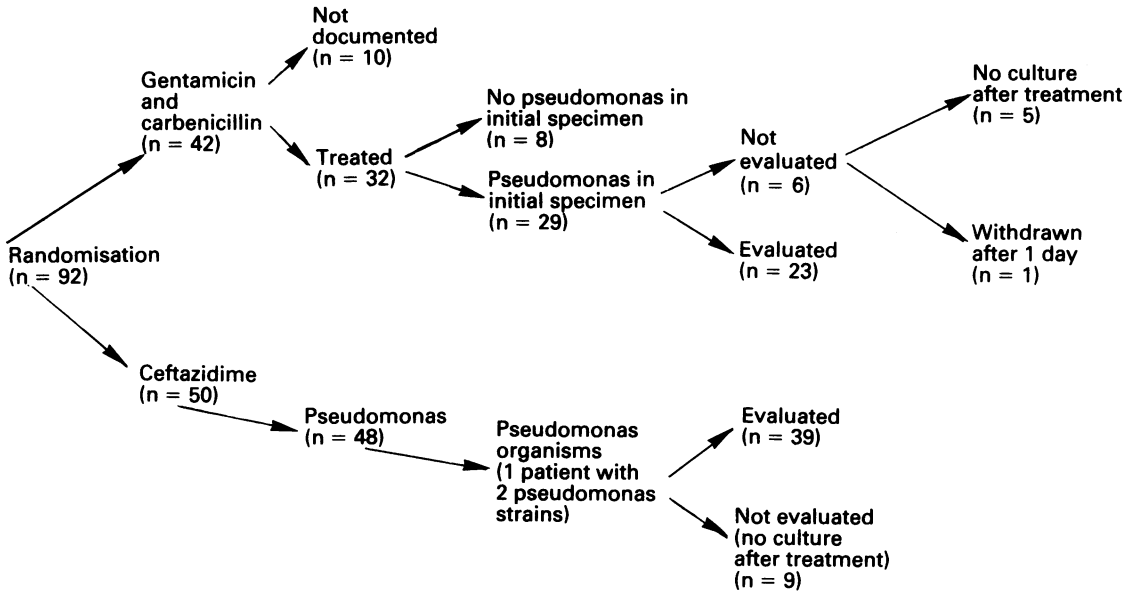
Samples of sputum were collected before and at the end of treatment and at two to four weeks and three months after completion of treatment. They were subjected to routine culture to identify the presence and strain of pseudomonas together with its sensitivity to ceftazidime, other cephalosporins, gentamicin, and carbenicillin. Mean inhibitory concentrations were also determined on some of the strains. Patients were considered to be bacteriologically assessable when pathogens were grown from pretreatment specimens and when post-treatment sputum was cultured in the laboratory.

Ceftazidime concentrations were measured at a single centre in sputum samples taken between two and six days after the start of treatment. These were kept frozen at −20°C and assayed within two weeks or kept for longer periods at −70°C until assay. They were then dispersed in 10% sputolysin (Cal-

Table 1 *Comparison of patients receiving gentamicin and carbenicillin (G/C) with patients receiving ceftazidime (CAZ)*

	G/C (n = 32)	*CAZ (n = 50)*
No (%) female	18 (56)	26 (52)
Mean (range) age (years)	15.5 (6–28)	16.2 (5–34)
No (%) taking antibiotics in previous 3 days	23 (72)	40 (80)
Mean (range) duration of treatment (days)	10.0 (1–18)	11.8 (7–17)

Flow diagram to illustrate randomisation and numbers of patients (n) and organisms evaluation in Tables 2 and 3.



biochem; Behring), and all samples were assayed microbiologically against the test strains *Proteus morganii* NCTC 235 in the range 0.1–5 mg/l as well as *Bacillus subtilis* 1904E for samples above 5 mg/l. Whenever enough material was available assays were done in duplicate.

Statistical analysis

Statistical analysis of overall clinical and bacteriological results and laboratory abnormalities was by contingency table testing using χ^2 tests confirmed by Fisher's exact test whenever small numbers of successes or failures occurred. Peak expiratory flow rate and changes in white cell counts during and after treatment were analysed by t tests and regression analysis.

Results

Patients and treatment

Table 1 shows the composition of the two groups of patients. There were 92 patients, 50 randomly allocated to receive ceftazidime and 42 to receive gentamicin and carbenicillin (fig). Two patients receiving ceftazidime and 10 receiving gentamicin and carbenicillin were not evaluated, one in each group because no initial sputum specimens were obtained and one in the group receiving ceftazidime because pseudomonas was not isolated from the initial sputum specimen. In addition, records of six patients receiving gentamicin and carbenicillin were lost and three other patients receiving gentamicin and carbenicillin were withdrawn because of initial resistance of pseudomonas to carbenicillin.

Gentamicin was given every eight hours in all patients with a total daily dose range of 4.8–9.1 mg/kg (mean of 6.3 mg/kg). In seven underweight patients who received only 60 mg gentamicin thrice daily the dose range was 5.1–7.0 mg/kg (6.0 mg/kg). Carbenicillin was given in total daily doses of 290–690 mg/kg (450 mg/kg). Twenty four patients received doses every six hours, five every four hours and two every eight hours. One patient received only a single dose of carbenicillin before being withdrawn from the study.

All patients but one in the group receiving ceftazidime were given the drug every eight hours. The daily dose was 86–231 mg/kg (mean of 151 mg/kg).

Sputum concentrations of ceftazidime

The mean ceftazidime concentration in 49 sputum samples from the patients treated with ceftazidime

Table 2 *Presence of pseudomonas in the sputum immediately after treatment with gentamicin and carbenicillin (G/C) or ceftazidime (CAZ)*

	G/C (n = 29)	*CAZ (n = 48)*
Number unassessable	6	9
Number available for assessment	23	39
Number (%) with pseudomonas absent	6 (26)	7 (18)
Number (%) with pseudomonas present	17 (74)	32 (82)

Table 3 *Eradication of organisms by antibiotic regimens. Patients receiving ceftazidime (CAZ) included 48 who were assessable but two pseudomonas species were grown from the sputum of one patient*

	G/C (n = 29)			*CAZ (n = 49)*		
	Succeed	*Fail*	*Not assessable*	*Succeed*	*Fail*	*Not assessable*
Pseudomonas:						
Aeruginosa	5	11	4	5	22	4
Unspecified or other species	1	6	2	3	10	5
Other organisms:						
Staphylococcus aureus	0	2	1	6	0	1
Haemophilus influenzae	3	1	0	4	0	2
Klebsiella pneumoniae	1	0	1			
Escherichia coli	0	0	1			

G/C = gentamicin and carbenicillin.

was 2.5 mg/l. The concentrations were similar to those recorded previously in patients with cystic fibrosis.[9]

Bacteriological results

The figure gives details of the isolation of pseudomonas from the sputum of the patients. Tables 2 and 3 show the bacteriological results of treatment. No pseudomonas was grown from the specimen taken immediately after treatment in six (26%) of 23 assessable patients receiving gentamicin and carbenicillin or seven (18%) of 39 receiving ceftazidime. Four of these patient in each group had sputum cultured at three months, but only one of the four in each group remained free from pseudomonas.

From Table 3 it can be seen that nine of 29 organisms recovered from patients receiving gentamicin and carbenicillin and 18 of 49 organisms from patients receiving ceftazidime were of a pseudomonas species other than aeruginosa or, more usually, were of unspecified type. The patients receiving gentamicin and carbenicillin were also infected by a total of 10 other organisms and those receiving ceftazidime by 13 other organisms. These organisms were eliminated in all 10 patients receiving ceftazidime from whom sputum was collected before and after treatment but in only four of seven assessable patients receiving gentamicin and carbenicillin. In particular, gentamicin and carbenicillin failed to eliminate *Staphylococcus aureus* in both assessable patients, whereas this organism was eliminated in all six assessable patients receiving ceftazidime ($p = 0.04$).

The sensitivity of pseudomonas to carbenicillin before treatment was assessed in 65 patients. In 47 (72%) the pseudomonas was sensitive to carbenicillin. All 69 initial isolates of pseudomonas were sensitive to ceftazidime and 63 (91%) of 69 initial isolates were sensitive to gentamicin. Resistance to carbenicillin was found in pseudomonas from four of the patients treated with gentamicin and carbenicillin and 13 of the 35 treated with ceftazidime for whom sensitivity data were available.

Only two of the 35 patients receiving ceftazidime whose pseudomonas was initially sensitive to ceftazidime yielded strains resistant to ceftazidime in the specimen taken after treatment. In both cases bacteriological typing showed that the strain of these resistant organisms was different from the strain isolated before treatment.

When the 29 patients receiving gentamicin and carbenicillin who had pseudomonas sensitive to gentamicin in their initial sputum culture were considered three had gentamicin resistant pseudomonas at the end of treatment. Of 26 patients receiving gentamicin and carbenicillin who had carbenicillin sensitive pseudomonas at the start, three yielded carbenicillin resistant pseudomonas in the specimen taken after treatment.

Clinical results

The overall condition of patients before treatment as assessed by the clinicians was similar in the two treatment groups and this improved during treatment in 25 (78%) of the 32 patients receiving gentamicin and carbenicillin and 48 (96%) of the 50 patients receiving ceftazidime ($p < 0.05$). There was no significant difference between the two groups in weight gain, fall in temperature, fall in total white blood cell count, or rise in peak expiratory flow rate during treatment. Nearly all symptoms and signs improved during treatment with both regimens.

Separate analysis of the clinical results, excluding those from the 13 patients receiving ceftazidime and the four receiving gentamicin and carbenicillin with carbenicillin resistant organisms, showed no difference between the treatment groups. Nine patients had two courses of antibiotics and three had three courses; six had two courses of ceftazidime and two had two courses of gentamicin and carbenicillin. There was no evidence that the second course of either antibiotic regimen was less effective, but *Pseudomonas aeruginosa* was not eliminated from

the sputum in either group of patients.

Assessment of progress during the first three months after the first course of treatment showed that 19 (59%) of 32 patients treated with gentamicin and carbenicillin but only 15 (30%) of 50 treated with ceftazidime were admitted to hospital, required intravenous antibiotics, or died ($p < 0.05$). In three patients receiving gentamicin and carbenicillin relapse occurred despite prophylactic inhalation of antibiotics active against pseudomonas.

Adverse effects

One patient treated with gentamicin and carbenicillin developed severe asthma after the first dose and was withdrawn from the study. Another patient in this group suffered a rash, arthralgia, and fever. Four patients in the same group developed thrombophlebitis at the site of intravenous infusion in the arm. Two patients receiving ceftazidime had a rash. Minor biochemical changes, mainly transient abnormalities shown by liver function tests, occurred in seven patients in each group.

Discussion

In view of the poor bacteriological results and the only temporary success of penicillins and aminoglycosides in the treatment of cystic fibrosis the role of the new cephalosporins has been under review. One of the most promising agents in vitro has been ceftazidime, which was found to have an MIC_{50} for *Pseudomonas aeruginosa* of 1 μg/ml compared with 2 μg/ml for gentamicin and 16 μg/ml for cefotaxime.[10] One report of ceftazidime in cystic fibrosis has shown that it produced clinical improvement on all but one of 15 occasions when it was used in patients with acute exacerbations of respiratory symptoms and pseudomonas infection.[11] Eradication of the organism from the sputum at the end of treatment had occurred in 22% of another series of patients.[7]

Most early reports of ceftazidime in cystic fibrosis described non-randomised trials of the drug alone or in combination. We have compared its use as a single agent with the widely used regimen of gentamicin and carbenicillin in an open randomised trial. Our results confirm that ceftazidime alone is at least as effective as a combination of gentamicin and carbenicillin. Moreover, it was significantly more successful than the combination in eradicating concomitant staphylococcal infection ($p < 0.05$). Side effects were uncommon, and intravenous bolus injection of this antibiotic was easier and more tolerable than intravenous infusion of carbenicillin over half an hour. As with most newly introduced antibiotics, a much smaller proportion of the organisms showed primary resistance compared with the primary resistance to carbenicillin of 28%. This incidence was higher than that of one recent study in which *Pseudomonas aeruginosa* from only one of 12 patients was resistant to both carbenicillin and azlocillin.[6] In another report, however, primary pseudomonas resistance to azlocillin and to piperacillin was lower than that to carbenicillin.[12] It is interesting that despite the presence of carbenicillin resistant organisms in four of the 30 patients treated with gentamicin and carbenicillin the bacteriological and clinical results of treatment with this combination were similar to those reported in earlier studies.[3 13]

This study has suffered from some of the deficiencies inherent in multicentre trials, including variation in the interpretation of the protocol between different centres and failure to adhere strictly to the protocol in all cases. These deficiencies contributed to the difference in numbers of patients in the two treatment groups. Although this difference was undesirable, there is no evidence that it influenced the results. Some bias in favour of ceftazidime may, however, have resulted from the chance difference in the mean duration of treatment with this drug (11.8 days) compared with that of gentamicin and carbenicillin (10 days).

Although the bacteriological evidence suggests that ceftazidime should be a useful antibiotic in acute respiratory exacerbations in patients with pulmonary pseudomonas infection, the organisms were eradicated from the sputum in only a minority of patients, and in most of these bacteriological relapse occurred within three months. In a three month follow up period 30% of this group of patients required readmission to hospital, relapsed immediately after treatment, or died compared with 59% of the patients given gentamicin and carbenicillin ($p < 0.05$). Possible reasons for the disappointingly temporary effect of both treatments include lack of penetration of the drug into pus and lung tissue where residual organisms may remain. The drugs may substantially reduce the population of organisms in the lung without completely eradicating them, as has been shown in previous trials.[7] Another explanation is that in some patients the lungs may be sterilised during the course of treatment but that recolonisation occurs after this.

Intravenous ceftazidime appears to be a promising treatment for patients with cystic fibrosis and pulmonary pseudomonas infections who develop acute exacerbations of their respiratory symptoms. What is now needed is an equally effective agent that may be given by mouth or by nebuliser over a longer period with the object of clearing the lungs of pseudomonas or at least of reducing the bacteriological load sufficiently to prevent further acute

exacerbations of respiratory symptoms.

This study was carried out at the following hospitals by clinicians and bacteriologists: London Chest Hospital (Dr DM Geddes); Brompton Hospital (Dr JC Batten, Dr ME Hodson); Hospital for Sick Children, London (Dr R Dinwiddie); Hospital for Sick Children, Tadworth (Dr MB Mearns, Dr Benton); Western Infirmary, Glasgow (Dr KE Berkin, Dr BHR Stack, Dr S Alcock); Royal Belfast Hospital for Sick Children (Dr OAB Redmond); Royal Aberdeen Children's Hospital (Dr G Russell, Dr DN Symon); Sydenham Children's Hospital (Dr P Wallis); Brompton Hospital, Frimley (Dr RK Knight); Raigmore Hospital, Inverness (Dr WD Murray); City Hospital, Edinburgh (Dr M Sudlow).

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References

1 Kulczycki LL, Murphy TM, Bellanti JA. Pseudomonas colonisation in cystic fibrosis. A study of 160 patients. *JAMA* 1978;**240**:30–4.

2 Beaudry PH, Marks MI, McDougall D, Desmond K, Rangel R. Is anti-Pseudomonas therapy warranted in acute respiratory exacerbations in children with cystic fibrosis? *J Pediatr* 1980;**97**:144–7.

3 Friis B. Chemotherapy of chronic infection with mucoid Pseudomonas aeruginosa in lower airways of patients with cystic fibrosis. *Scand J Infect Dis* 1979;**11**:211–7.

4 Davis SD, Burns WT. Effects of sputum from patients with cystic fibrosis on the activity in vitro of 5 antimicrobial drugs on Pseudomonas aeruginosa. *Am Rev Respir Dis* 1978;**117**:176–8.

5 Malmborg AS, Alfredsson H, Kusoffsky E, Strandvik B. Azlocillin and gentamicin in respiratory tract infections with Pseudomonas aeruginosa in patients with cystic fibrosis. *Scand J Infect Dis* 1981; suppl 29:64–9.

6 Penketh ARL, Hodson ME, Gaya H, Batten JC. Azlocillin compared with carbenicillin in the treatment of bronchopulmonary infection due to Pseudomonas aeruginosa in cystic fibrosis. *Thorax* 1984;**39**:299–304.

7 Mastella G, Agostini M, Barlocco G, *et al.* Alternative antibiotics for the treatment of pseudomonas infections in cystic fibrosis. *J Antimicrob Chemother* 1983;**12** (suppl A):297–311.

8 Scribner RK, Marks MI, Weber AH, Tarpay MM, Welch DF. Activities of various β-lactams and aminoglycosides alone and in combination against isolates of Pseudomonas aeruginosa from patients with cystic fibrosis. *Antimicrob Agents Chemother* 1982;**21**:939–43.

9 Strandvik B, Malmborg A-S, Alfredson H, Ericsson A. Clinical results and pharmacokinetics of ceftazidime treatment in patients with cystic fibrosis. *J Antimicrob Chemother* 1983;**12** (suppl A):283–7.

10 O'Callaghan CH, Acred P, Harper PB, Ryan DM, Kirby SM, Harding SM. GR20263, a new broad-spectrum cephalosporin with antipseudomonal activity. *Antimicrob Agents Chemother* 1980;**12**:876–83.

11 Kercsmar CM, Stern RC, Reed MD, Myers CM, Murdell D, Blumer JL. Ceftazidime in cystic fibrosis: pharmacokinetics and therapeutic response. *J Antimicrob Chemother* 1983;**12** (suppl A):289–95.

12 Møller NE, Eriksen KR, Feddersen C, *et al.* Chemotherapy against Pseudomonas aeruginosa in cystic fibrosis. A study of carbenicillin, azlocillin or piperacillin in combination with tobramycin. *Eur J Respir Dis* 1982;**63**:130–9.

13 Hodson ME, Wingfield HJ, Batten JC. Tobramycin and carbenicillin compared with gentamicin and carbenicillin in the treatment of infection with Pseudomonas aeruginosa in adult patients with cystic fibrosis. *Br J Dis Chest* 1983;**77**:71–7.