Use and control of cephalosporins

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It is now over 20 years since Professor Brotzu recovered the mould *Cephalosporium acremonium* from Sardinian sewage and found that it produced antibiotic material. Figure 1 represents a simplified cephalosporin family tree. The first antibiotic to be isolated from the mould was cephalosporin N, an acyl derivative of 6-aminopenicillanic acid, susceptible to the action of staphylococcal penicillinase and much less active against Gram-positive bacteria than benzyl penicillin. Cephalosporin P consists of one major component and at least four minor components: its major component is a steroid related chemically to, but considerably less active than, fusidic acid. The most important antibiotic elaborated by the cephalosporium mould is cephalosporin C, but it is only produced in minute quantities. It is from cephalosporin C that the

semi-synthetic cephalosporins have been derived. Several hundred analogues have been produced by substitution of different chemical groups at the 7 and 3 position (R_1 and R_2 in the diagram) of the cephalosporin nucleus and have been investigated for antimicrobial activity. Four cephalosporins have been extensively studied in various parts of the world—cephaloridine, cephalothin, cephalixin, and cephaloglycine—and of these the first three drugs are now available commercially in Britain and it is with them that this paper is concerned. Cephaloridine has been available since 1964 and cephalothin and cephalixin much more recently.

Antibacterial Spectrum

The antibacterial spectrum of the three cephalo-

CEPHALOSPORIUM ACREMONIUM

Fig. 1 *Derivatives of Cephalosporium acremonium.*

sporins is similar but they differ markedly in their activity. In general, cephaloridine is the most active and cephalixin the least active though unexpected differences may be found for some organisms. Cephalosporins exhibit a wide range of activity against Gram-positive and Gram-negative bacteria but are ineffective against *Pseudomonas aeruginosa*, *Enterobacter*, indole-positive *Proteus* and *Bacteroides*, and of limited activity against *Haemophilus influenzae* and *Streptococcus faecalis*. A large number of minimum inhibitory concentrations (MICs) have been determined for the three cephalosporins in parallel on strains recently isolated at St. Thomas's Hospital. Both heavy and light inocula of the organisms were used on solid media: a heavy inoculum consisted of approximately 0.02 ml of a broth culture containing 10^8 organisms per ml and a light inoculum consisted of a 10^{-4} dilution of the above.

COAGULASE-POSITIVE STAPHYLOCOCCI

The results obtained for 53 coagulase-positive staphylococci are shown in Figure 2. Cephaloridine is the most active cephalosporin against penicillin-sensitive staphylococci: its activity compares favourably with that of penicillin. Cephalothin is only marginally less active than cephaloridine, with cephalixin least active. The majority of strains have MICs of cephalixin about 30 times those of

cephaloridine. With all three cephalosporins there is very little difference between the MIC value obtained with heavy and light inocula for penicillin-sensitive staphylococci.

However, the results are rather different for the penicillinase-producing strains: some of the strains investigated were resistant to streptomycin, tetracycline, and erythromycin as well as to penicillin. With cephaloridine, there is a marked inoculum effect: the MICs obtained with a light inoculum are very much less than those with a heavy inoculum. The inoculum effect is much less evident with cephalothin and cephalixin. Against a heavy inoculum of penicillinase-producing staphylococci, cephalothin is the most active cephalosporin due to its greater stability to staphylococcal penicillinase. Cephalixin is also more stable to staphylococcal penicillinase than cephaloridine but is intrinsically less active than cephalothin.

Twenty-three strains of methicillin-resistant staphylococci have also been investigated for cephalosporin sensitivity. With a light inoculum the majority of these strains were inhibited by $1.5 \mu\text{g}$ cephaloridine per ml and by $0.78 \mu\text{g}$ cephalothin per ml, but when a heavy inoculum of the organism was used, all strains were highly resistant to cephaloridine but much less resistant to cephalothin. All strains tested were highly resistant to cephalixin both with heavy and light inocula. Some degree of

		μg antibiotic per ml												total
		inoculum	25	12.5	6.25	3.1	1.56	0.78	0.39	0.19	0.09	0.04	0.02	
PENICILLIN SENSITIVE	cephaloridine	heavy										•••••	•••••	17
		light										•••••	•••••	17
	cephalothin	heavy						•	•	•	•••••	•••••	•••••	17
		light						•	•	•	•••••	•••••	•••••	17
	cephalexin	heavy		••		•••••	••							17
		light		•	••	••••	••••	•••••	•					17
PENICILLIN RESISTANT	cephaloridine	heavy	••	••••	•••••	••	••••	•••••	•••••	••••				36
		light								•••••	•••••	•••••	•	36
	cephalothin	heavy			•	••••	••••	•••••	•••••	••••	•••••	•••••	•••••	36
		light								•••••	•••••	•••••	•••••	36
	cephalexin	heavy	••	••••	••••	•••••	•••••	•••••	•••••					36
		light				••••	•••••	•••••	•		•••	••		36

Fig. 2 Effect of inoculum size on cephalosporin MIC for coagulase positive staphylococci.

cross-resistance occurs between methicillin and all three cephalosporins; this seems to be most marked between cephalixin and methicillin and least evident between cephalothin and methicillin. Kind, Kestle, Standiford, Freeman, and Kirby (1969a) have demonstrated that cephalixin, like methicillin, can produce resistant variants of staphylococci on repeated exposure of sensitive strains to either drug *in vitro*. These variants are seen as small colonies within the zone of inhibition around the antibiotic disc. In contrast, they never found isolated colonies within the zones of inhibition around discs of cephaloridines or cephalothin and colonies selected from around the inhibition zones remained sensitive to these antibiotics and methicillin even after serial transfer.

GRAM-NEGATIVE BACILLI AND STREPTOCOCCUS FAECALIS

The MIC results obtained using a light inoculum of 100 strains of *Escherichia coli* with the cephalosporins are shown in Figure 3. Cephaloridine is the most active; over 60% of the strains were inhibited by 3.9 μg per ml or less whereas only 30% were inhibited by the same amount of cephalothin or cephalixin. The results for 85 strains of *Klebsiella* (all non-motile and lysine decarboxylase positive) are shown in Figure 4 (light inoculum). There is little to choose

between the activity of the three cephalosporins against *Klebsiellae*, with cephalothin perhaps marginally best. The indole-positive *Proteus* seem to be universally resistant to cephalosporins but the majority of *Proteus mirabilis* strains are sensitive, with cephaloridine and cephalothin about equally active and cephalixin least so. The results obtained using light inocula of 66 strains of *Proteus mirabilis* are shown in Figure 5.

The MICs for 100 strains of *Streptococcus faecalis* (see Fig. 6) were lower for cephaloridine than for cephalothin, but with values of 7.8 to 15.6 μg per ml for the majority of strains using light inocula, neither antibiotic could be considered very active. Most strains were highly resistant to cephalixin and over 50% of these required 125 μg per ml for inhibition.

A decrease in inoculum size almost always led to a decrease in cephalosporin MIC for the Gram-negative bacilli. The actual degree of decrease in MIC obtained was rather variable and was sometimes as much as a hundredfold or even more. For any individual organism, however, the inoculum effect was not necessarily of the same magnitude for each cephalosporin tested. It is perhaps associated with the type and amount of β -lactamase produced by each organism. Figure 7 compares the effect of inoculum size on the MIC of cephaloridine and cephalixin for 76 strains of *Escherichia coli*.

Fig. 4

Fig. 5

Fig. 6 Sensitivity of 100 strains of *Streptococcus faecalis* to cephalosporins.

Fig. 7 Effect of inoculum size on MIC of cephalosporins for 76 strains of *E. coli*.

Fig. 7

The effect of inoculum size on cephalosporin MIC is really only of therapeutic importance for penicillinase-producing staphylococci. Since cephaloridine is to some extent destroyed by penicillinase it is probably not a suitable drug to treat severe infection caused by staphylococci producing large amounts of the enzyme. Although in theory if enough cephaloridine was given it might be effective, cephalothin would be the better drug in this situation.

Pharmacological Properties (see Fig. 8)

MODE OF ACTION

All cephalosporin derivatives act by inhibition of

bacterial cell wall synthesis and are bactericidal; in general, the level of drug required to achieve a bactericidal effect for most organisms is only two to three times that required for bacteriostasis.

ROUTE OF ADMINISTRATION

Cephaloridine and cephalothin are only very poorly absorbed from the gut and must be given by injection which may be intramuscular or intravenous. The serum levels achieved with cephaloridine are about 50% higher than those reached with an equivalent dose of cephalothin. Cephalexin and cephaloglycine are absorbed from the gut and cephaloxin in particular is very well absorbed; it is available for oral

	Cephaloridine	Cephalothin	Cephalexin
Mode of action	Inhibition of Cell Wall Synthesis		
Route of administration	Intramuscular Intravenous	Intramuscular Intravenous	Oral
Binding to serum protein	20%	65%	13–19%
Excretion	Mostly by glomerular filtration; minimal tubular secretion	Mainly by tubular secretion	Secreted and reabsorbed by renal tubule
Probenecid	Minimal effect	Blocks secretion	Blocks secretion
Toxicity	Dose-related nephrotoxicity, possibly enhanced by frusemide	Rashes Pain on intramuscular injection. Thrombophlebitis on intravenous injection. Positive direct Coombs. ? ? nephrotoxic	Diarrhoea, vulvovaginitis

Fig. 8 Comparison of cephalosporins.

Fig. 9 Serum cephalexin levels in fasting volunteers following a dose of 250 mg.

administration only. In a recent study in our laboratory, 16 fasting volunteers (laboratory technicians) were given an oral dose of 250 mg of cephalexin and their serum levels were measured over the next four hours; not only was the peak serum level obtained very variable in individuals (levels from 2.7 to 19.0 μg cephalexin per ml) but the time taken to reach the peak level was also very variable. Four of the absorption curves obtained are shown in Figure 9. Since the volunteers all took the oral dose under identical conditions it is difficult to explain these discrepancies but other workers have described similar findings (Brumfitt, 1970). Moreover this variability of time and height of peak serum level occurred with both preparations of cephalexin (Keflex and Ceporex).

BINDING TO SERUM PROTEIN

Cephalosporins do not all bind to serum proteins to the same extent. Cephaloridine and cephalexin are only minimally bound but a large proportion of cephalothin is bound. Although the degree of protein binding found with cephalothin is much greater than that of ampicillin or methicillin, it is still considerably less than that of cloxacillin. The actual figures given in the literature for protein binding of cephalosporins are rather variable but Kind, Kestle, Standiford, and Kirby (1969b) quote values of 20% for cephaloridine, 13-19% for cephalexin, and 65% for cephalothin.

EXCRETION

Cephalosporins are almost entirely excreted by the kidney, but they are not all handled by the kidney in the same way. Cephaloridine is excreted mainly by glomerular filtration with only a minimal amount of tubular secretion; about 75% of a single dose of cephaloridine can be recovered from the urine in about eight hours (Weinstein and Kaplan, 1970). The effect of probenecid on cephaloridine serum levels is negligible unless large doses of cephaloridine are given.

Cephalothin is excreted mainly by tubular secretion and this can be effectively blocked by probenecid. However, about 20% of the cephalothin appearing in the urine is present as the weakly antibacterial metabolite desacetyl cephalothin due to drug metabolism in the liver. Cephalothin is excreted rather more rapidly than cephaloridine: over 95% of an administered dose can be recovered from the urine within six hours (Weinstein and Kaplan, 1970). Cephalexin is secreted and reabsorbed by the renal tubule and its excretion, like that of cephalothin, can be blocked by probenecid. Excretion of cephalexin is rapid and 80-100% of an

administered dose can be recovered from the urine in six hours.

TOXICITY

All three cephalosporin derivatives are of relatively low toxicity; they should, however, be administered with caution to patients with a history of penicillin hypersensitivity, since about 10% of such patients will also prove hypersensitive to cephalosporins.

Nephrotoxicity

Cephaloridine is known to be a potentially nephrotoxic drug both in laboratory animals and in man. In animals, the dose required to produce renal damage varies widely with different species and the female rabbit is the most sensitive. Cephaloridine causes necrosis of the proximal cells of the kidney tubules (Atkinson, Caisey, Currie, Middleton, Pratt, Sharpe, and Tomich, 1966a; Atkinson, Currie, Davis, Pratt, Sharpe, and Tomich, 1966b). Lawson, Macadam, Singh, Gavras, and Linton (1970) have demonstrated that in the rabbit the nephrotoxic effect of cephaloridine is enhanced by the diuretic frusemide and suggested that this may also be true in man. Foord (1969) reported 36 cases in which cephaloridine was suspected of causing renal failure in man; in nine of these the renal function was known to be impaired before administration of the drug and in 13 others it was probably impaired. In the eight patients in Foord's series whose serum cephaloridine level was measured, figures from 40 to 1,500 μg per ml were recorded. Seven patients also received frusemide. The nephrotoxic effect of cephaloridine on the proximal renal tubule is probably dose-related and it is most likely to occur if serum levels exceed 100 to 150 μg per ml. It is potentially reversible on stopping the drug.

Figure 10 summarizes a case of probable cephaloridine nephrotoxicity seen at St. Thomas's Hospital. The patient was a 54-year-old woman with diabetes who was operated on for replacement of the mitral and aortic valves on 16 July 1970. She received prophylactic cephaloridine in a dose of 500 mg six hourly intravenously.

Her renal function was known to be impaired at the time of operation and blood urea levels of 50 to 85 mg per 100 ml had been recorded over the previous year. She was treated postoperatively with intravenous frusemide on several occasions. Her urine output started to fall on the seventh postoperative day and at the same time the blood urea concentration rose to nearly 400 mg per 100 ml. On the 11th postoperative day she became shocked and was found to have *Enterobacter aerogenes* in her blood and the same organism was recovered, amongst others, from her sputum. The *Enterobacter*

Fig. 10 Possible cephaloridine nephrotoxicity in a 54-year-old woman following aortic and mitral valve replacement.

was highly resistant to cephaloridine which was then discontinued. She was dialysed by the peritoneal route from the 12th to the 26th postoperative day and her renal function recovered its preoperative level. The septicaemia was successfully treated initially with gentamicin and later with intravenous and then oral trimethoprim and sulphamethoxazole. It is possible that the complicating septicaemia may have contributed to the renal failure, but it is also highly likely that the combination of renal impairment, cephaloridine, and frusemide were at least partly to blame, since her urine output fell and her blood urea rose several days before she became shocked. Unfortunately cephaloridine serum levels were not estimated, but two days after stopping the drug there was considerable residual cephaloridine in her serum as this interfered with the assay of gentamicin.

Cephalothin causes minimal swelling of the proximal tubular epithelium in rabbits whereas the equivalent dose of cephaloridine produces tubular necrosis (Perkins, Apicella, Lee, Cuppage, and Saslaw, 1968). Lawson *et al* (1970) did not, however, find that frusemide, given in conjunction with cephalothin to rabbits with kidneys minimally damaged by glycerol, produced further nephro-

toxicity. Despite the encouraging reports from animal work there are now suggestions that cephalothin, like cephaloridine, may be nephrotoxic in man. In reported cases the dose of cephalothin has usually been high but it has not always been easy to assess to what extent cephalothin alone was responsible for the deteriorating renal function as other factors were frequently involved (Rahal, Meyers, and Weinstein, 1968; Turcotte, Herrmann, Haig, O'Dell, Cerny, and Greene, 1970; Pickering, Spooner, de Quesada, and Cade, 1970). There are as yet no reports suggesting that cephalixin is nephrotoxic.

Positive direct Coombs test

A positive direct Coombs test is found not infrequently in patients being treated with cephalothin, particularly when the serum levels of the drug are very high or when the patient has some degree of renal impairment or hypoalbuminaemia (Gralnick, Wright, and McGinniss, 1967; Molthan, Reidenberg, and Eichman, 1967). It is not associated with haemolytic anaemia and seems to be of no clinical significance but may interfere with cross-matching of blood in the laboratory. A positive direct Coombs test has also been reported in patients on cephaloridine (Fass, Perkins, and Saslow, 1970) but the

8% incidence with this drug was much lower than the reported series for cephalothin where the incidence varied from 38 to 75%. There was no association with impaired renal function, hypoalbuminaemia, or high dosage therapy. Cephalixin may also cause a positive direct Coombs test though, as with cephaloridine, this is uncommon. Of 36 patients treated with cephalixin for recurrent urinary tract infection at St. Thomas's Hospital, only one developed a positive direct Coombs test during therapy.

Other toxic effects

Cephalothin, unlike cephaloridine, is painful on intramuscular injection particularly with a 1 g dose and may be intolerable by this route after several days and intravenous injection may cause thrombophlebitis. Cephalothin may also cause neutropenia. Cephalixin, like most oral broad-spectrum antibiotics, may cause gastrointestinal disturbances but some of the nausea and vomiting reported in earlier clinical trials may well have been attributable to the unpleasant smell and taste of the initial clinical trial material. Vulvovaginitis has been reported by Leigh, Faiers, and Brumfitt (1970) and by Faireley (1970) as a troublesome side effect of cephalixin.

CEPHALOSPORINS IN RENAL FAILURE

Since there exists a possible danger of nephrotoxicity, particularly with cephaloridine, it is important to know how patients whose renal function is grossly impaired excrete cephalosporins. Table I shows the effect of uraemia and of dialysis on the serum half-life of cephaloridine, cephalothin, and cephalixin.

In patients with normal renal function the serum half-life of cephaloridine and cephalixin is similar (1.2 hours and 1.5 hours) whereas cephalothin is excreted more rapidly with a serum half-life of 0.5 hours. In uraemia (that is in patients whose creatinine clearance is less than 3 ml per min), the serum half-life of cephaloridine and cephalixin is greatly

increased (23 hours and 21.5 hours). The serum half-life of cephalothin in uraemia is prolonged (2.9 hours) but to a much lesser extent than cephaloridine or cephalixin. It follows, therefore, that the dosage schedule for cephaloridine and cephalixin will require greater modification in renal failure than that for cephalothin. During dialysis the serum half-life of cephaloridine and cephalixin is markedly reduced strongly suggesting that they are both largely removed by dialysis. This is probably also true for cephalothin. There is also a tendency for the cephaloridine serum half-life to fall with increasing duration of maintenance haemodialysis (Curtis and Marshall, 1970). The reasons for this are not known but presumably extrarenal mechanisms of cephaloridine degradation become increasingly important with increasing duration of maintenance haemodialysis. The interval between doses of the cephalosporins will need to be much shorter when a patient is being dialysed than during the periods between dialysis, or therapeutic levels of the drug may not be maintained. It may well be necessary to monitor serum levels in uraemic patients who are treated with cephalosporins.

Assay of Cephalosporins

The overall methods are set out in Table II. Cephalosporins can readily be assayed microbiologically by the plate method with reasonable accuracy. Cephaloridine is undoubtedly the easiest of the three drugs to assay and gives large clear-cut zones of inhibition on Oxoid DST agar using *Bacillus subtilis* ATCC 6633. *Sarcina lutea* can also be used, but in our experience gives less distinct zone margins. Stock solutions of cephaloridine can be stored at 4°C for at least a week without loss of potency and possibly longer.

Cephalothin can be assayed by the method described for cephaloridine but tends to give smaller zones of inhibition. It is important to remember also

Serum Half Life	Cephaloridine	Cephalothin	Cephalixin
Normal renal function	1.5 ± 0.3 hr ^a 1.52 hr ^a	0.5 ± 0.3 hr ^a 0.85 hr ^a	1.2 ± 0.4 hr ^a
Uraemia: not on haemodialysis ¹	23 ± 3 hr ^a 20 hr ^a 10.4 hr ⁴	2.8 ± 0.9 hr ^a 2.9 hr ^a	21.5 ± 1.9 hr ^a 21.8 hr ^a
Uraemia: on haemodialysis ¹	3.5 hr ⁴	?	4.5 ± 0.9 hr ^a 4.6 ± 0.7 hr ^a

Table I *Cephalosporins in renal failure*

¹Uraemia = Creatinine clearance < 3ml/min

^aFrom Kabins *et al* (1970)

²From Kunin and Atuk (1966)

⁴From Curtis and Marshall (1970)

⁵From Bailey *et al* (1970)

	Agar	Assay Organism	Buffer	Stability in Solution
Cephaloridine	DST	<i>B. subtilis</i> / <i>S. lutea</i>	pH 7	Stable
Cephalothin	DST	<i>B. subtilis</i> / <i>S. lutea</i>	pH 7	Stable
Cephalexin	Special ¹	<i>B. subtilis</i> / <i>S. lutea</i>	pH 6	Unstable

Table II Plate assay of cephalosporins

¹ Oxoid agar No. 3	1.2%
Oxoid peptone	0.5%
Oxoid lab-lemco	0.3%
Sodium citrate	1.0%

that one is in fact assaying a mixture of cephalothin and its descetyl metabolite using a cephalothin standard. The standard solutions for assay of cephalothin in serum must be made up in human serum as it is so highly bound to protein, but for cephaloridine and cephalexin comparable results are obtained whether serum or buffer is used to make up the standard solutions. Stock solutions of cephalothin can be stored at 4°C for at least a week.

Cephalexin assay is unsatisfactory if DST agar is used: the best results are obtained with the 'special agar' which is recommended by Glaxo Laboratories. Stock solutions of cephalexin seem to deteriorate rapidly if stored for any length of time and it is always advisable to make up fresh stock solutions for each assay.

Clinical Use of Cephalosporins

Cephaloridine is now well established as a valuable bactericidal parenteral antibiotic, with activity against a wide range of organisms. It is the most active of the available cephalosporin derivatives though less stable to staphylococcal penicillinase than cephalothin or cephalexin. The serum levels achieved with cephaloridine are considerably higher than those with cephalothin in equivalent dosage. Despite the possible risk of nephrotoxicity with cephaloridine it should not be withheld from a patient with impaired renal function if it is therapeutically indicated, but caution should be exercised in devising the dosage schedule and serum levels of the drug monitored where necessary. It should not be given in conjunction with frusemide.

Cephalothin is not only less active than cephaloridine, except against penicillinase-producing staphylococci, but it also has the added disadvantage of producing pain on intramuscular injection whereas cephaloridine is relatively painless. Although it was claimed initially that cephalothin did not cause renal damage it now appears that this drug, like cephaloridine, may cause tubular necrosis. If a parenteral cephalosporin is clinically indicated cephaloridine should be given in preference to cephalothin.

Cephalexin is the only oral cephalosporin available in the UK: it is unfortunately much less active than cephaloridine and against most organisms is less active than cephalothin also. However, it is very well absorbed and causes relatively few side effects with to date no reports of nephrotoxicity.

Numerous clinical trials have now been carried out on cephalexin and it has been given for a wide variety of infections; it is, however, probably most useful for treatment of urinary infections (particularly *Klebsiella* and *Citrobacter*) and for some patients with penicillin hypersensitivity for whom an oral drug is indicated. Cephalexin is at present extremely expensive and in most of the situations where it might be clinically indicated there is nearly always a much cheaper, equally effective alternative drug available.

I would like to thank Eli Lilly and Glaxo for supplies of cephalexin and for financial support for some of this work, Mr M. Braimbridge for permission to study his patient, Miss C. Jenkins, AIMLT, for very efficient technical assistance, and Dr I. Phillips for helpful advice and criticism.

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