A survey of the sensitivity of fresh clinical isolates to cefuroxime and other antibiotics

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SUMMARY The sensitivities to cefuroxime and cephradine of potentially pathogenic bacteria isolated in two British general hospitals comprising 900 beds have been assessed. In a three-month period, 2537 strains were studied; 30 µg cefuroxime discs were used with 2511 strains, and cephradine discs of the same strength were used with 2525 strains. The organisms were also examined routinely for sensitivity to other antibiotics. Overall, 91.7% of the isolates were sensitive to cefuroxime and 85.8% were inhibited by cephradine, the differences in percentage strain susceptibility to cefuroxime and cephradine being mainly a result of the greater activity of cefuroxime against the Gram-negative bacteria. The wide antibacterial effectiveness of cefuroxime should make it a useful antibiotic for the treatment of serious infections including those conditions in which the causative organism has not been identified.

Cefuroxime is a new semisynthetic cephalosporin antibiotic (O'Callaghan *et al.*, 1976) which has marked stability to staphylococcal penicillinase and to a wide range of β-lactamases produced by Gram-negative bacteria. The antibiotic penetrates the permeability barrier provided by the cell envelope of most Gram-negative bacteria, the major exception being *Pseudomonas aeruginosa*, which is impermeable to many antibiotics. Cefuroxime is also active against the penicillin-binding proteins of Gram-negative bacteria, with highest affinity for penicillin-binding protein 3 (Spratt, 1975) which is involved in cell division (N. A. C. Curtis, unpublished data). The contribution that cefuroxime can make in treating infections is dependent upon such factors as its β-lactamase stability, cell penetrability, the incidence of infection with particular bacteria, and the comparison with current antibiotics. The aim of this study was to assess the usefulness of cefuroxime through analysis of sensitivity tests carried out on consecutive bacterial isolates from all specimens over a predetermined period.

Material and methods

For three months, from 1 May to 31 July 1977, a

prospective survey was conducted on all potentially pathogenic bacteria isolated from clinical specimens sent to the hospitals' bacteriology laboratory. No special precautions were taken to exclude identical bacteria from different or the same sources. Clinicians were not encouraged to submit more frequent specimens than was their normal practice. The source of the specimen was recorded (Table 1) and whether they originated from in- or out-patients.

Table 1 Sources of bacteria isolated and the proportion sensitive to cefuroxime

Source of specimen	Numbers of organisms		
	Isolated	% of total	% Sensitive to cefuroxime
Wound	765	30.2	89.9
Nose	38	1.5	100
Throat	85	3.4	97.6
Ear	52	2.0	94.2
Eye	179	7.1	95.5
Blood	25	0.9	96.0
Sputum	126	5.0	97.6
Urine	1126	44.4	91.0
Urethra	44	1.7	83.7
High vaginal swab	66	2.6	97.0
Faeces	4	0.2	100*
CSF	1	0.03	100*
Bone and fractures	24	0.9	95.8
Not specified	2	0.07	100*

*Based on very small numbers.

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ISOLATION AND IDENTIFICATION OF BACTERIA

Organisms were isolated by the techniques routinely used in the study of clinical specimens. Staphylococci were subdivided into *Staphylococcus aureus* or *Staphylococcus epidermidis* according to their deoxyribonuclease activity. Lancefield's grouping was performed on β -haemolytic streptococci; anaerobic Gram-positive cocci were denoted as anaerobic streptococci whereas those requiring only reduced oxygen tension were referred to as microaerophilic streptococci. Clostridia were identified using the methods recommended by Cowan and Steel (1965) and neisseria were screened utilising the serum-free medium of Flynn and Waitkins (1972). Aerobic Gram-negative rods were grouped into lactose and non-lactose fermenters and further subdivided by additional biochemical reactions. In most cases, identification was confirmed by use of the API 20E system. Anaerobic Gram-negative rods were identified using the API 20A system.

ANTIBIOTIC SUSCEPTIBILITY TESTING

Antibiotic sensitivities were examined using Oxoid diagnostic sensitivity test (DST) agar; where nutritionally demanding organisms were tested, blood or chocolate agar with a DST agar base was used, each plate containing 12.5 ml of medium. One colony was emulsified in 2 ml peptone water, and a loopful of the suspension was inoculated onto the sensitivity plate and spread with a dry swab. The plates were incubated without prediffusion. Daily control tests were performed with *Staph. aureus* NCTC 6571, *Escherichia coli* NCTC 10418, and *Ps. aeruginosa* NCTC 10662. Isolates were deemed sensitive or resistant by comparison with the control method described by Garrod *et al.* (1973), except that the term 'moderately resistant' was not used, organisms falling into this category being regarded as resistant. A range of Oxoid Multodisks and Mast and Oxoid single discs was used. Sensitivity to cefuroxime and cephradine was assessed using single 30 μ g Oxoid discs, and the cultures were recorded as either sensitive or resistant. The other antibiotics used were penicillin 1.5 μ g, gentamicin 10 μ g, cotrimoxazole 25 μ g, cephaloridine 15 μ g or 25 μ g, tetracycline 10 μ g or 50 μ g, erythromycin 10 μ g, lincomycin 2 μ g, metronidazole 5 μ g, clindamycin 2 μ g, kanamycin 5 μ g or 30 μ g, colistin 10 μ g or 25 μ g, methicillin 25 μ g, and carbenicillin 100 μ g. When two strengths of disc are mentioned, the disc with the greater potency was used for urine isolates.

Results

During the survey period, 2537 bacterial strains sus-

pected of being pathogenic were examined for antibiotic sensitivity. Of the strains isolated, 2511 were examined for cefuroxime sensitivity and 2525 for sensitivity to cephradine. Examination of the remaining strains, most of which were staphylococci or streptococci, was inadvertently omitted.

The types of isolates and their incidence are illustrated in the Figure. The largest single group of organisms was *E. coli* (765 isolates, of which two gave atypical reactions), representing 30.2% of the total bacterial ecology. The next most frequent isolate was *Staph. aureus* (359 strains), accounting for 14.2% of the total population. Other major groups included *Klebsiella* spp (7.6%) and *Proteus* spp (9.6%). Bacteroides and pseudomonas were isolated with relative infrequency, being 2.0% and 1.7% respectively of the population; they generally came from wound swabs but pseudomonas also originated from urine specimens.

Figure Distribution of 2537 isolates over a three-month period from two British general hospitals. The percentages represent the incidence of the various bacteria.

SENSITIVITIES

Of the 2511 isolates examined, 2302 (91.7%) were sensitive to cefuroxime, and of the 2525 tested with cephradine, 2167 (85.8%) were sensitive. The sensitivities to cefuroxime of organisms from each type of clinical specimen are given in Table 1. There were no appreciable differences between those bacteria isolated from inpatients and those from outpatients. Although cefuroxime was more consistently active than cephradine against both Gram-positive and

Gram-negative bacteria, the difference was more marked for the Gram-negative strains, 90.2% of which were sensitive to cefuroxime compared with only 82.7% for cephradine. Cefuroxime was active against 93.8% of the Gram-positive strains, cephradine against 90.3%. In the whole survey there were only 18 strains sensitive to cephradine and resistant to cefuroxime but about nine times as many (168) resistant to cephradine but sensitive to cefuroxime. Most of these latter strains were Enterobacteriaceae. It was thought that the strains accidentally omitted from the sensitivity testing would not significantly have altered the overall results; only 11 organisms were not examined with either cephalosporin and, of those tested with only one cephalosporin, all were sensitive. Cefuroxime and cephradine were more comprehensively tested than the other antibiotics, the activity of which can therefore be compared with the cephalosporins only within specific groups of bacteria.

The results obtained for the staphylococci are shown in Table 2. All but occasional strains of *Staph. aureus* were sensitive to the cephalosporins, methicillin, and erythromycin, but four-fifths of isolates were resistant to benzylpenicillin, including those from outpatients. *Staph. epidermidis* strains were

cephalosporin sensitive with few exceptions, but methicillin, fusidic acid, and erythromycin were active against less than 90% of isolates.

Streptococcus pneumoniae strains were fully sensitive to the cephalosporins and to many other antibiotics (Table 3). All *Streptococcus mitis* (viridans group) strains were cefuroxime sensitive but not all strains were susceptible to the other antibiotics. All but one of the strains tested of streptococci of Lancefield's groups A, B, C, F, and G were sensitive to the first and second generation cephalosporins and benzylpenicillin; the exception, in group F, was sensitive to ampicillin. All 62 group B β -haemolytic streptococci, which were included in this group, were cephalosporin and penicillin sensitive.

There were 171 isolates of *Streptococcus faecalis* and two of Lancefield's group D, the total forming the fourth largest group of the survey. Cefuroxime was active against two-thirds of the strains, cephradine against half. The remaining 47 miscellaneous streptococci consisted of non-haemolytic aerobes (4), microaerophilic strains (17), and those not typing as groups A-D, F, or G (26). At least 95% were sensitive to the majority of antibiotics (Table 3). One strain of corynebacterium was tested in the survey; it was isolated in heavy growth from an eye swab.

Table 2 Sensitivities of 516 staphylococci to seven antibiotics

Organism	Number isolated	Antibiotic						
		Cefuroxime	Cephradine	Penicillin G	Methicillin	Erythromycin	Fusidic acid	Tetracycline
<i>Staph. aureus</i>	359	100 (351)	99.4 (358)	20.1 (358)	99.7 (354)	90.8 (358)	96.9 (350)	83.5 (358)
<i>Staph. epidermidis</i>	157	96.7 (153)	96.1 (155)	34.4	88.5	80.1 (156)	88.2 (153)	60.3 (156)
Total	516	99.0 (504)	98.4 (513)	24.5 (515)	96.3 (511)	87.5 (514)	94.2 (503)	76.5 (514)

Figures in parentheses indicate the number of strains tested whenever these were less than the number isolated.

Table 3 Sensitivities of 483 aerobic streptococci to six antibiotics

Organism	Number isolated	Antibiotic					
		Cefuroxime	Cephradine	Penicillin G	Ampicillin	Erythromycin	Tetracycline
<i>Strep. pneumoniae</i>	57	100	100	100 (54)	100	100	100
<i>Strep. mitis</i> (viridans group)	53	100 (51)	96.1 (51)	94.0 (50)	100	98.0 (49)	75.5
β -haemolytic streptococci Lancefield's groups A, B, C, F, G	153	99.3	99.3	99.3 (149)	100	97.0 (133)	48.4
<i>Strep. faecalis</i> + Lancefield's group D streptococci	173	67.9 (168)	49.1 (171)	1.8 (169)	98.3 (172)	83.3 (168)	38.7
Other aerobic streptococci	47	95.7 (46)	97.8 (46)	93.6	97.9	95.2 (4)	83.0
Total	483	88.0 (475)	81.1 (477)	62.9 (469)	99.0 (482)	92.2 (449)	57.3

Figures in parentheses indicate the numbers of strains tested whenever these were less than the number isolated.

However, it proved to be a culture of antibiotic-sensitive *Coryne xerosis*.

Table 4 shows the susceptibility to eight antibiotics of the enterobacteria isolated. The majority of *Klebsiella* spp were identified as *K. pneumoniae* and only one *K. ozaenae* was isolated. The indole-positive proteus comprised isolates of *Pr. morganii* (7), *Pr. vulgaris* (5), *Pr. rettgeri* (2), and *Pr. inconstans* (*stuartii*) (2), and cefuroxime was active against twice as many of these strains as was cephradine. There were seven *Serratia liquefaciens*, eight *Serratia marcescens*, and five unspecified *serratia*; neither of the cephalosporins was active against any *Serr. marcescens* strains but gentamicin was active against all. Only one strain each of *Enterobacter aerogenes* and *Enterobacter agglomerans* were identified, 33 typing as *Enterobacter cloacae*. The other six were not fully identified. Over two-thirds of the *Enterobacter* spp were sensitive to cefuroxime but only about half to cephradine. More strains of *Citrobacter freundii* were sensitive to cefuroxime than to gentamicin. The pathogens isolated from the four faecal specimens were *Shigella flexneri*, *Shigella sonnei* (2), and *Salmonella enteritidis*, all four being sensitive to most of the antibiotics tested although one *Sh. sonnei* was resistant to ampicillin. Overall, none of the other antibiotics approached the level of activity of the cephalosporins or gentamicin, and the most potent antibacterial agents against the Enterobacteriaceae were cefuroxime, with 93.5% tested strains sensitive, and gentamicin which was active against 97.8% of isolates.

The most frequently encountered aerobic Gram-negative organisms, apart from enterobacteria, were *Haemophilus influenzae* (54 strains), *Acinetobacter*

spp (19 strains, of which 16 were positively identified as *A. calcoaceticus*), and *Neisseria gonorrhoeae* (14 strains). All of the gonococci were sensitive to cefuroxime, cephradine, ampicillin, cotrimoxazole, and tetracycline. All of the *H. influenzae* were sensitive to cefuroxime, ampicillin, and tetracycline but only 83.3% were sensitive to cephradine. Cotrimoxazole was tested against only 38 strains; all were sensitive. Cefuroxime was active against only 11 acinetobacter strains but all were fully sensitive to gentamicin and tetracycline. Other strains isolated included an *Aeromonas hydrophila* and an *Alcaligenes* sp; the former was sensitive to cefuroxime but not to cephradine, the latter was resistant to both. The 42 pseudomonads, including one each of *Ps. fluorescens* and *Ps. maltophilia*, and 40 *Ps. aeruginosa*, were resistant to the cephalosporins but sensitive to gentamicin.

Table 5 demonstrates the results for the anaerobes. Metronidazole was tested against 43 of the 50 bacteroides isolates and was active against all of them. These included strains which were not further typed and which could therefore have been *Bact. fragilis*. Nonetheless, cefuroxime fared better against the bacteroides of unknown species than against the *Bact. fragilis* strains. Clindamycin was tested against only 24 strains of bacteroides but was fully active. The only other antibiotic with any significant success against bacteroides was erythromycin but several antibiotics enjoyed reasonable activity against the clostridium isolates and the anaerobic streptococci (Table 4).

Discussion

Cefuroxime was active against the vast majority of

Table 4 Sensitivities of 1302 Enterobacteriaceae to eight antibiotics

Organism	Number isolated	Antibiotic							
		Cefuroxime	Cephradine	Gentamicin	Ampicillin	Cotrimoxazole	Carbenicillin	Colistin	Tetracycline
<i>E. coli</i>	765	97.2 (762)	92.4 (762)	98.8 (764)	77.1 (763)	93.9 (758)	79.5 (764)	99.9 (763)	82.3 (764)
<i>Klebsiella</i> spp	193	93.8	93.3	97.9 (192)	2.6	74.1	7.3	99.0 (192)	71.4 (168)
<i>Pr. mirabilis</i>	228	94.3	78.9	98.7	89.3 (225)	82.8 (227)	95.2	0.9 (226)	3.1 (160)
Indole-positive proteus	16	68.8	37.5	87.5	25.0	68.8	81.3	12.5	43.8
<i>Serratia</i> spp	20	25.0	20.0	100	15.0	25.0	25.0	80.0	20.0
<i>Enterobacter</i> spp	41	70.7	51.2	97.6	34.1	68.3	47.5 (40)	97.6	53.7
<i>Citrobacter freundii</i>	35	80.0	45.7	74.3	14.3	45.7	42.9	97.1	44.1 (34)
<i>Shigella</i> spp	3	100	100	100	66.7	100	100	100	66.7
<i>Salm. enteritidis</i>	1	100	100	100	100	100	100	100	100
Total	1302	93.5 (1299)	85.8 (1299)	97.8 (1300)	63.5 (1297)	85.5 (1294)	68.8 (1300)	80.8 (1297)	66.7 (1207)

Figures in parentheses indicate numbers of strains tested whenever these were less than the number isolated.

Table 5 Sensitivities of 105 anaerobic organisms to eight antibiotics

Organism	Number isolated	Antibiotic							
		Cefuroxime	Cephadrine	Metronidazole	Erythromycin	Tetracycline	Clindamycin	Penicillin	Ampicillin
<i>Bact. fragilis</i>	27	69.2 (26)	76.9 (26)	100 (23)	85.2	81.5	100 (10)	3.7	25.9
<i>Bacteroides</i> spp	23	95.2 (21)	86.4 (22)	100 (20)	100	69.6	100 (14)	21.7	69.6
<i>Clostridium</i> spp	16	93.8	87.5	83.3 (6)	87.5	87.5	0 (1)	87.5	100 (15)
Anaerobic streptococci	39	97.4	97.4	100 (33)	94.9	71.8	100 (19)	94.9	97.4
Total	105	89.2 (102)	88.3 (103)	98.8 (82)	92.8	76.2	97.7 (44)	54.3	73.1 (104)

Figures in parentheses indicate the numbers of strains tested whenever these were less than the number isolated.

both Gram-positive and Gram-negative aerobic and anaerobic bacteria encountered in our study. In many instances, over 90% of the isolates from each genus were sensitive, and the antibiotic was inactive only against *Ps. aeruginosa*. By comparison with cephradine, cefuroxime was more frequently active against organisms of almost all genera. Our survey yielded similar results on an epidemiological basis to the one carried out by Jones *et al.* (1977), which covered nearly 6000 strains isolated in four laboratories situated in three widely separated areas of the USA. In both surveys, for example, *E. coli* accounted for over 30% of isolates. The main differences were a larger proportion of Gram-positive cocci, especially streptococci, and anaerobes in the Southend survey and a greater incidence of enterobacteria and pseudomonas in the USA. The bacteriological data in such surveys do show, however, geographical variation, and the results obtained at Southend may not fully reflect the situation in other general hospitals.

The disc-diffusion method of sensitivity testing does not distinguish degrees of antibiotic susceptibility, but, in general, cefuroxime appears to be more active gravimetrically than cephradine even against sensitive organisms. Disc sensitivity testing, therefore, by a first-generation cephalosporin cannot be reliably used to indicate sensitivity to second-generation cephalosporins.

Cefuroxime is highly stable to most β -lactamases, including the Gram-negative class III enzymes mediated by R-factors (Richmond and Sykes, 1973) and the enzymes produced by staphylococci. This is reflected in the Southend sensitivity patterns for the isolates likely to contain these enzymes. Occasionally, class III β -lactamases are found in haemophilus and neisseria but were not specifically sought in any of the strains isolated in our survey. Also found are enzymes from class I, and cefuroxime is extremely stable to most of them, although some strains of *Bact. fragilis*, usually *Bact. fragilis* ssp *fragilis*, *Ser-*

ratia spp, and indole-positive proteus can produce enzymes capable of hydrolysing cefuroxime, and this renders such strains resistant to its antibacterial action. Thus one reason why one-third of the *Bact. fragilis*, one-third of the indole-positive proteus, and three-quarters of the *Serratia* strains were insensitive to the cephalosporins was presumably production of a class I β -lactamase. The percentage of *Bact. fragilis* strains resistant to cefuroxime varies considerably among centres (Eykyne *et al.*, 1976; Norrby *et al.*, 1976; Jones *et al.*, 1977) and the proportion of species producing this type of class I enzyme is probably the single most important factor responsible for the variabilities.

Cefuroxime has been shown to penetrate rapidly into the cell walls of most Gram-negative bacteria, and this is a contributory feature of its antibiotic effectiveness, but *Ps. aeruginosa* is relatively impermeable to many antibiotics, including cefuroxime. Despite the stability that cefuroxime has in the presence of the various β -lactamases that this organism can produce, notably the inducible, chromosomally mediated cephalosporinase described by Sabath and colleagues (1965) and the class III TEM-type enzymes, the species is not susceptible. The inactivity of cefuroxime against one-third of *Strep. faecalis* strains may be due partly to poor penetration of the antibiotic into the cell wall.

Bacteria from a wide variety of clinical specimens were generally found to be sensitive to cefuroxime (Table 1). However, as other antibiotics were not universally tested in our study, partly because of presumed inactivity, overall comparisons cannot readily be made. Nonetheless it appears that cefuroxime exhibits wider antibacterial activity against current clinical isolates than any other antibiotic in our test schedule. Activity against two-thirds of *Strep. faecalis* strains and many isolates of *Bacteroides* spp make significant and clinically important contributions to the wide antibacterial cover afforded by cefuroxime.

This broad-spectrum activity should make it useful for the treatment of infections requiring prompt parenteral therapy when the causative pathogen has not been identified and is not thought likely to be *Ps. aeruginosa*. In our survey only one of 25 isolates from blood culture was resistant to cefuroxime. Encouraging therapeutic results in septicaemia have been reported by several authors (Gobernado *et al.*, 1977; Shah *et al.*, 1977; Geddes *et al.*, 1978).

The excellent *in vitro* activity of cefuroxime against *Staph. epidermidis* and *Strep. mitis* suggests that it may be useful in infections by those bacteria and especially in cases of endocarditis. The low toxicity of cefuroxime would be an additional benefit in these circumstances. All of the Lancefield's group B β -haemolytic streptococci were sensitive to cefuroxime, which promises that it may find a place in perinatal medicine although the fulminating course of neonatal infections by group B streptococci is a disadvantage for all antibiotics.

Therapeutic concentrations of cefuroxime occur in the cerebrospinal fluid in meningitis (Kuzemko and Walker, 1977; Norrby *et al.*, 1977; Renlund and Pettay, 1977; Wilkinson *et al.*, 1977). Excellent activity against *Strep. pneumoniae*, *Neisseria meningitidis* (Fallon and Brown, 1979), *H. influenzae*, and *E. coli* make it an appropriate choice for meningitis in any age group.

In many acute chest infections the pathogen is not isolated. However, cefuroxime has good activity against the most likely bacteria, for example, *H. influenzae* and *Strep. pneumoniae*; in our survey it was active against 97.6% of 126 isolates from sputum and has been found to be effective clinically (Miki, 1977; Pines *et al.*, 1977; Seed *et al.*, 1977; Bax *et al.*, 1979). *Klebsiella* spp, although resistant to many antibiotics, are frequently sensitive to cefuroxime. It has been shown to be successful clinically in epidemics caused by such strains (Bint *et al.*, 1979).

Cefuroxime shows great potential for a variety of infections in different sites, and initial clinical studies (Copland, 1977; Daikos *et al.*, 1977; Graninger *et al.*, 1977; Scott, 1977; Geddes *et al.*, 1978) have so far borne out this promise.

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