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New cephalosporins and related compounds

Recently cephalosporins and related compounds have been developed that possess high activity against enterobacteria and at least some activity against *Pseudomonas aeruginosa*. The properties of several such compounds were reported at the 11th International Congress of Chemotherapy held in October 1979 (the proceedings being published as *Current Chemotherapy and Infectious Disease* by the American Society for Microbiology, Washington, D.C. 1980). It seems, therefore, an appropriate time to take stock of the situation.

Cefotaxime (HR 756) was developed first and can be used as a standard against which other compounds are judged. Cefotaxime has a broad spectrum of activity with, in addition to high activity against all species of enterobacteria, *Haemophilus* spp. and *Neisseria* spp., activity against *Acinetobacter* spp., most isolates of *Ps. aeruginosa* and some other pseudomonads, most anaerobes and most staphylococci and streptococci, but not methicillin-resistant staphylococci or *Streptococcus faecalis*. However it is less active than cephaloridine against staphylococci and streptococci. Some doubt remains about the usefulness of its activity against the *Bacteroides fragilis* group since, although it is slightly more active than cefoxitin when a small inoculum (10⁵ colony forming units or less) is tested, there is rather more inoculum effect than with cefoxitin (Wise et al., 1978; King et al., 1980). Very large inoculum effects on the activity of cefotaxime against enterobacteria have been observed, but the mechanism and relevance of this phenomenon are not yet known (Neu et al., 1979a; King et al., 1980). Cefotaxime resembles cefuroxime in stability to β-lactamases, being resistant to most but hydrolysed by the enzymes from *B. fragilis* and *Proteus vulgaris* (Fu & Neu, 1978; King et al., 1980). High blood levels of cefotaxime can be achieved; reported concentrations after an intravenous dose of 2 g range from 40 to 300 mg/l with a half-life of 1 to 16 h (Lüthy et al., 1979; Gialdroni Grassi et al., 1980; Ho et al., 1980; Wittmann & Schassan, 1980). Some of the discrepancies may be accounted for by difficulties in assaying the compound. Like cephalothin, cefotaxime is deacetylated in the body (White et al., 1980; Wise et al., 1980). The desacetyl metabolite is 4- to 16-fold less active than cefotaxime against some organisms (*Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Staphylococcus aureus*) and virtually inactive against others (*Proteus mirabilis*, *Ps. aeruginosa*) (Wise et al., 1980). The deacetylation also occurs in vivo in serum or urine, rapidly if haemolysis has occurred (White et al., 1980). Thus misleading results may be obtained if samples are stored under unsuitable conditions before assay. Clinical experience with cefotaxime is limited, but impressions so far are favourable (Clumeck et al., 1980; McKendrick, Geddes & Wise, 1980; Newsom et al., 1980). LY 127935 (6059S) is not a cephalosporin but is a 1-oxa-β-lactam compound with the 7-methoxy group characteristic of the cephamycins. Its antibacterial activity is similar to...
that of cefotaxime, though it is less active against Gram-positive organisms and more active against B. fragilis (Barza et al., 1979; Neu et al., 1979b; Wise, Andrews & Bedford, 1979; Warren et al., 1980). It was highly resistant to all the \( \beta \)-lactamases tested by Warren et al. (1980). LY127935 gives similar blood levels to cefotaxime in man (Israel et al., 1980). Some of the volunteers in this study experienced brief periods of diarrhoea that subsided during continued administration of the drug. toxigenic Clostridium difficile was isolated from one but no toxin was detected in the stool (Allen et al., 1980; Israel et al., 1980).

Cefoperazone (T 1551) is less active than cefotaxime or LY127935 against most Gram-negative organisms but is more active than these compounds against Ps. aeruginosa (Neu et al., 1979c; Hall, Opfer & Gerding, 1980; Martinez-Beltran et al., 1980; Trager et al., 1980). Little has been reported about its stability to \( \beta \)-lactamases but it is hydrolysed by TEM-1 (Williams & Williams, 1980) & PSE-4 (Dalglish) enzymes (Shannon et al., 1980). Blood levels of 16 to 70 mg/l have been reported after intravenous injection of 2 g (Hara et al., 1980). Since cefoperazone-resistant variants of Ps. aeruginosa can be readily selected in vitro, it has been suggested that the drug should be used in combination with an aminoglycoside (Slack et al., 1980).

Other new cephalosporins have been reported briefly. FK 749 (Takaya et al., 1980) and GR 20263 (Harper, Kirby & O’Callaghan, 1980) apparently resemble cefotaxime. YM 09330, a cephamycin, seems to be somewhat less active (Yano et al., 1980). SM-1652 has activity against Ps. aeruginosa comparable to that of cefuroladin but possesses relatively more activity than cefuroladin against enterobacteria (Komatsu et al., 1980). Ceforanide (Weaver, Le Blanc & Bodey, 1979) and cefazaflur (Aswapokee & Neu, 1979) are less active than other new cephalosporins.

It cannot be disputed that several of these new cephalosporins have very promising antibacterial activity but it is less clear what their clinical role should be. There is probably a small but definite role for an anti-pseudomonal cephalosporin such as cefsulodin. Other compounds may have a role against enterobacteria, especially aminoglycoside-resistant strains, gonococci and H. influenzae, and also perhaps for the treatment of mixed infections. However, one hopes that the high cost of these compounds will act as a deterrent to widespread use since this can be expected to lead to an increase in the number of resistant isolates. Such isolates are not unknown even though these new cephalosporins are not yet widely used.

K. P. SHANNON
Department of Microbiology,
St. Thomas’s Hospital Medical School,
London SE1 7EH, England

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