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# Comparison of In Vitro Activity of FCE 22101, a New Penem, with Those of Other β-Lactam Antibiotics

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The in vitro activity of FCE 22101, a new semisynthetic penem derivative, was compared with that of ceftriaxone, moxalactam, imipenem (formerly imipemide, *N*-formimidoyl thienamycin, or MK 0787), cefuroxime, ceftazidime, and other β-lactams, when appropriate, against 472 recent isolates and known β-lactam-resistant strains. The minimum inhibitory concentrations of FCE 22101 against 90% of the members of the family *Enterobacteriaceae, Haemophilus influenzae, Staphylococcus aureus*, Lancefield group D streptococci, and *Bacteroides* spp. were between 0.5 and 4 μg/ml. Methicillin-resistant strains of *Staphylococcus aureus* were susceptible. Ninety percent of the *Neisseria gonorrhoeae* and *Streptococcus pneumoniae* strains were susceptible to 0.25 μg of FCE 22101 per ml. *Pseudomonas aeruginosa* strains were resistant to FCE 22101 (minimum inhibitory concentration, >128 μg/ml). The susceptibility of known, characterized β-lactamase-producing strains of the *Enterobacteriaceae* suggested that FCE 22101 is resistant to many β-lactamases. Generally, FCE 22101 was slightly less active than imipenem, moxalactam, ceftriaxone, and ceftazidime against members of the *Enterobacteriaceae* and considerably more active than the cephalosporins (including moxalactam) against *Staphylococcus aureus*. The human serum protein binding of FCE 22101 was about 40%, and human serum had little effect on the activity.

In recent years, there has been great interest in exploiting the biochemical modification of β-lactam compounds. One area which so far has been less than fruitful is the development of penems. Although many, including Sch 29,482, have been synthesized (2, 3, 7, 9), not one has been fully developed. FCE 22101 (Fig. 1) is a new penem having the formula sodium (5*R*, 6*S*, 8*R*)-6-hydroxyethyl-2-carbamoyloxymethyl-2-penem-3-carboxylate and differs from Sch 29,482, which has an ethylthio group in the 2 position (6). In this study, we compared FCE 22101 with other β-lactams against a wide range of recent clinical isolates and also against strains known to be resistant to certain of these agents. The effect of serum on the activity of the compound was also studied.

## MATERIALS AND METHODS

**Strains and antimicrobial agents.** Of the 472 strains examined in this study, 449 were recent clinical isolates from this hospital and are listed in Table 1 according to strain and number. The remaining 23 were well characterized β-lactamase producers and other resistant strains donated from various sources. The antibiotics, of known potency, were obtained from the following pharmaceutical companies: FCE 22101 from Farmitalia Carlo Erba, Milan, Italy; ceftriaxone from Roche Products, Welwyn Garden City, England; moxalactam from Lilly Research Centre, Windlesham, England; imipenem (formerly imipemide, *N*-formimidoyl thienamycin, or MK 0787) from Merck Sharp & Dohme, Hoddesdon, England; cefuroxime and ceftazidime from Glaxo Research, Greenford, England; carbenicillin, penicillin, and ampicillin from Beecham Research Laboratories, Brentford, England.

**Methods.** The susceptibilities of the strains to the compounds were studied by a routine agar plate dilution method with Iso-Sensitest agar (pH 7.2) (Oxoid Ltd., Basingstoke, England), which was supplemented as follows: 5% whole horse blood to support growth of streptococci (including *S. pneumoniae*); a Levinthal preparation (5) to support the growth of *Haemophilus influenzae*; a Mast Laboratories Ltd. (Liverpool, England) SAF (sulfonamide antagonist-free) medium supplemented with 5% horse blood to support the growth of *Neisseria gonorrhoeae*. For the *Bacteroides* spp., Wilkins-Chalgren (Oxoid) agar was used.

Inocula were prepared as follows. For all strains except streptococci (including *Streptococcus pneumoniae*), *Neisseria gonorrhoeae, Haemophilus influenzae*, and *Bacteroides* spp., the organisms were grown overnight in nutrient broth yielding a viable count of about $10^9$ CFU/ml. Streptococci (including Lancefield group D) were grown in Todd-Hewitt broth; *Haemophilus influenzae, Streptococcus pneumoniae*, and *Neisseria gonorrhoeae* were grown in Levinthal broth; and *Bacteroides fragilis* was grown in Wilkins-Chalgren broth, each giving comparable viable counts.

The inocula were obtained by transferring 1 μl of an undiluted or a 1:100 dilution of the overnight culture to the surface of the antibiotic-containing medium by a Denley multipoint inoculating device (Denley-Tech Ltd., Billingshurst, England). The final inocula on the plates were therefore $10^4$ and $10^6$ CFU/ml. Incubation was for 24 h in air at 37°C (except for *Haemophilus influenzae* and *Neisseria gonorrhoeae* when 10% $CO_2$ was added). The dilution, inoculation, and incubation of the *Bacteroides* spp. were performed in an anaero-

TABLE 1. MICs inhibiting cumulative percentage of isolates

| Organism (no. of isolates) | Antibiotic | MIC (μg/ml) | | |
|---|---|---|---|---|
| | | Range | 50% | 90% |
| *Escherichia coli* (50) | FCE 22101 | 0.25–1 | 0.5 | 0.5 |
| | Ceftriaxone | <0.015–8 | 0.03 | 0.25 |
| | Moxalactam | 0.03–16 | 0.06 | 0.25 |
| | Imipenem | 0.06–1 | 0.12 | 0.5 |
| | Cefuroxime | 0.25–32 | 4 | 8 |
| | Ceftazidime | 0.03–>128 | 0.12 | 4 |
| *Klebsiella* sp. (50) | FCE 22101 | 0.5–1 | 0.5 | 1 |
| | Ceftriaxone | 0.015–4 | 0.06 | 0.5 |
| | Moxalactam | 0.03–1 | 0.06 | 0.12 |
| | Imipenem | 0.12–1 | 0.25 | 0.25 |
| | Cefuroxime | 0.5–128 | 2 | 16 |
| | Ceftazidime | <0.015–4 | 0.06 | 0.25 |
| *Enterobacter* spp. (10, including 4 *E. aerogenes*, 6 *E. cloacae*) | FCE 22101 | 0.5–8 | 2 | 4 |
| | Ceftriaxone | 0.12–16 | 0.12 | 2 |
| | Moxalactam | 0.06–4 | 0.12 | 1 |
| | Imipenem | 0.12–1 | 0.25 | 0.5 |
| | Cefuroxime | 4–128 | 8 | 16 |
| | Ceftazidime | 0.12–8 | 0.25 | 0.5 |
| *Proteus mirabilis* (50) | FCE 22101 | 1–4 | 1 | 2 |
| | Ceftriaxone | <0.015–0.12 | <0.015 | <0.015 |
| | Moxalactam | 0.06–0.12 | 0.06 | 0.06 |
| | Imipenem | 0.12–8 | 2 | 4 |
| | Cefuroxime | 1–>128 | 0.5 | 4 |
| | Ceftazidime | 0.03–0.12 | 0.03 | 0.06 |
| Indole-positive *Proteus* spp. (46, including 25 *P. vulgaris*, 18 *P. morganii*, 3 *P. rettgeri*) | FCE 22101 | 1–4 | 2 | 4 |
| | Ceftriaxone | <0.015–1 | 0.015 | 0.25 |
| | Moxalactam | 0.06–16 | 0.12 | 4 |
| | Imipenem | 0.25–16 | 2 | 4 |
| | Cefuroxime | 1–>128 | 32 | >128 |
| | Ceftazidime | 0.03–2 | 0.03 | 0.25 |
| *Serratia* spp. (17, including 15 *S. marcescens*, 2 *S. liquefasciens*) | FCE 22101 | 1–8 | 2 | 4 |
| | Ceftriaxone | <0.015–1 | 0.12 | 0.25 |
| | Moxalactam | 0.06–4 | 0.25 | 0.25 |
| | Imipenem | 0.12–4 | 0.25 | 4 |
| | Cefuroxime | 4–>128 | >64 | >128 |
| | Ceftazidime | 0.05–8 | 0.12 | 0.25 |
| *Providencia stuartii* (18) | FCE 22101 | 0.5–2 | 1 | 2 |
| | Ceftriaxone | 0.015–0.12 | 0.06 | 0.12 |
| | Moxalactam | 0.03–0.25 | 0.06 | 0.12 |
| | Imipenem | 0.12–2 | 1 | 2 |
| | Cefuroxime | 0.25–64 | 1 | 16 |
| | Ceftazidime | 0.06–1 | 0.12 | 0.5 |
| *Acinetobacter anitratum* (8) | FCE 22101 | 0.12–2 | 1 | 2 |
| | Ceftriaxone | 0.5–16 | 8 | 16 |
| | Moxalactam | 2–32 | 32 | 32 |
| | Imipenem | 0.06–0.25 | 0.12 | 0.25 |
| | Cefuroxime | 1–32 | 32 | 32 |
| | Ceftazidime | 1–16 | 4 | 16 |

TABLE 1—*Continued*

| Organism (no. of isolates) | Antibiotic | MIC (μg/ml) | | |
|---|---|---|---|---|
| | | Range | 50% | 90% |
| *Pseudomonas aeruginosa* (48) | FCE 22101 | 0.5–>128 | 128 | >128 |
| | Ceftriaxone | 1–64 | 4 | 32 |
| | Moxalactam | 0.06–64 | 8 | 32 |
| | Imipenem | 0.25–8 | 1 | 4 |
| | Cefuroxime | 8–>128 | >128 | >128 |
| | Ceftazidime | 0.06–4 | 1 | 32 |
| | Carbenicillin | 8–>128 | 64 | >128 |
| *Staphylococcus aureus* (30, including 10 methicillin-resistant isolates) | FCE 22101 | 0.06–2 | 0.12 | 0.5 |
| | Ceftriaxone | 2–>128 | 16 | 32 |
| | Moxalactam | 4–64 | 16 | 64 |
| | Imipenem | 0.06–1 | 0.06 | 0.12 |
| | Cefuroxime | 0.5–>128 | 4 | 32 |
| | Ceftazidime | 8–64 | 16 | 64 |
| *Streptococcus pneumoniae* (17) | FCE 22101 | 0.015–0.25 | 0.03 | 0.25 |
| | Ceftriaxone | ≤0.008–0.06 | ≤0.008 | 0.06 |
| | Moxalactam | 1–8 | 1 | 8 |
| | Imipenem | ≤0.008–0.06 | ≤0.008 | 0.06 |
| | Cefuroxime | ≤0.008–0.5 | 0.015 | 0.25 |
| | Ceftazidime | 0.06–2 | 0.12 | 2 |
| | Penicillin | ≤0.008–0.12 | ≤0.008 | 0.12 |
| *Haemophilus influenzae* (34, including 11 β-lactamase-positive isolates) | FCE 22101 | 0.25–1 | 1 | 1 |
| | Ceftriaxone | ≤0.008–0.06 | ≤0.008 | 0.6 |
| | Moxalactam | 0.03–2 | 0.06 | 2 |
| | Imipenem | 4–16 | 8 | 16 |
| | Cefuroxime | 0.5–16 | 1 | 8 |
| | Ceftazidime | 0.03–1 | 0.12 | 1 |
| | Ampicillin | 0.25–32 | 1 | 8 |
| *Neisseria gonorrhoeae* (23, including 11 β-lactamase-positive isolates) | FCE 22101 | ≤0.008–0.5 | 0.06 | 0.25 |
| | Ceftriaxone | ≤0.008–≤0.008 | ≤0.008 | ≤0.008 |
| | Moxalactam | ≤0.008–0.12 | 0.03 | 0.06 |
| | Imipenem | ≤0.008–2 | 0.06 | 0.25 |
| | Cefuroxime | ≤0.008–0.12 | 0.015 | 0.12 |
| | Ceftazidime | ≤0.008–0.06 | ≤0.008 | 0.06 |
| | Penicillin | 0.03–16 | 0.5 | 4 |
| *Bacteroides* spp. (29) | FCE 22101 | 0.015–1 | 0.03 | 0.5 |
| | Ceftriaxone | 0.5–>128 | 8 | >128 |
| | Moxalactam | 0.5–>128 | 4 | 64 |
| | Imipenem | 0.06–8 | 0.5 | 1 |
| | Cefuroxime | 1–>128 | 8 | 64 |
| | Ceftazidime | 2–>128 | 8 | >128 |
| | Penicillin | 4–>128 | 8 | >128 |

bic cabinet with an atmosphere of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. The minimum inhibitory concentration (MIC) of the antibiotic, against all organisms, was defined as that concentration (in micrograms per milliliter of agar) at which there was a reduction (by counting) to 10 or fewer colonies in the original inoculum. In the case of a higher inoculum, a faint haze of growth was ignored.

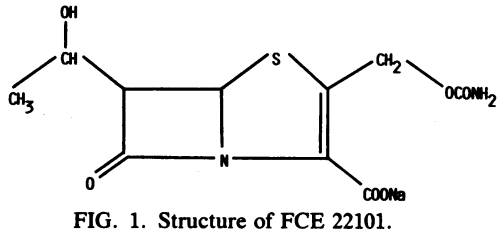


FIG. 1. Structure of FCE 22101.

The effect of human serum on the activity of FCE 22101 was studied by using two strains each of *Escherichia coli, Klebsiella* spp., *Proteus mirabilis, Staphylococcus aureus* (one strain of which was methicillin resistant), and Lancefield group D streptococci. An overnight broth culture (1 ml) of these strains was inoculated into Iso-Sensitest broth with 0, 20, and 70%

pooled human serum and decreasing concentrations of FCE 22101. The final inoculum was about $10^5$ CFU/ml. After 24 h of incubation at 37°C in air, the MIC was defined as the concentration of FCE 22101 at which there was no visible growth. The broths were then subcultured (0.01 ml transferred onto nutrient agar) and incubated for an additional 24 h. The minimum bactericidal concentration (MBC) of FCE 22101 was defined as the lowest concentration in the original broth at which there was no growth after subculture. This was calculated to be equivalent to a lethality rate of 99.9%.

The protein binding of FCE 22101 in human serum was estimated by an ultrafiltration technique (4), using an Amicon (Amicon Corp., Lexington, Mass.) Centriflo cone with a molecular weight exclusion of 50,000. The concentrations of FCE 22101 used were 5, 100, and 200 μg/ml. The ultrafiltrate (after a pH adjustment with $CO_2$ gas) was assayed by a microbiological technique against standards prepared in phosphate-buffered saline, pH 6.5 (the pH of the ultrafiltrate after the addition of $CO_2$). The indicator organism was a strain of *Staphylococcus aureus* F208, and the medium was Oxoid antibiotic medium no. 1.

## RESULTS

The results obtained for 429 isolates tested at an inoculum of $10^4$ CFU/ml are summarized in Table 1. FCE 22101 had a high degree of activity against members of the family *Enterobacteriaceae*; in general it was comparable to or slightly less active than imipenem, moxalactam, ceftazidime, and ceftriaxone. Exceptions to this pattern were the high activity of ceftriaxone against the *Proteus* spp. and the eightfold-greater activity of imipenem and ceftazidime (compared with FCE 22101) against *Enterobacter* spp. FCE 22101 and imipenem were about eightfold less active than ceftriaxone and moxalactam against *Serratia* spp. and *Providencia stuartii* but were more active than cefuroxime against those strains. Five strains of *Citrobacter freundii*, two of *Salmonella typhi*, three of *Salmonella* spp., and five of *Shigella sonnei* (not shown in Table 1) were also tested, and the MICs of FCE 22101 were either 0.5 or 1 μg/ml, except for one strain of *Citrobacter freundii* (MIC, 4 μg/ml). Of note was the narrow range of MICs of FCE 22101 among members of the *Enterobacteriaceae*, with the other antimicrobial agents showing a greater spread of susceptibilities.

An increase in inoculum to $10^6$ CFU/ml when members of the *Enterobacteriaceae* were tested resulted in at most a twofold decrease in susceptiblity to FCE 22101, moxalactam, imipenem, ceftriaxone, and ceftazidime; a greater effect was seen with *Klebsiella* spp., *Serratia* spp., indole-positive *Proteus* spp., and *Enterobacter* spp. when tested against cefuroxime.

Against *Acinetobacter anitratum*, FCE 22101 and imipenem displayed high activity. Against *Pseudomonas aeruginosa*, the activity of FCE 22101 was comparable to that of carbenicillin and was 64-fold less than that of imipenem.

Table 2 shows the susceptibilities of nine known β-lactamase-producing strains of *Enterobacteriaceae*, at two inocula, classified by the method of Richmond and Sykes (8). Cefuroxime was not active against groups I and IV strains, and ceftriaxone was not active against the group I strains. The other agents were active and had little effect when the inoculum was increased from $10^4$ to $10^6$ CFU/ml, suggesting that little β-lactamase hydrolysis was occurring.

Against *Staphylococcus aureus*, FCE 22101 showed activity similar to that of imipenem. The mode MIC of FCE 22101 against the 10 methicillin-resistant strains was 0.25 μg/ml (range, 0.12 to 2 μg/ml); the mode MIC of the 20 methicillin-susceptible strains was 0.12 μg/ml (range, 0.06 to 0.5 μg/ml). Similar results were obtained with imipenem, but with the other antimicrobial agents, the mode MIC for the methicillin-resistant strains was markedly higher than that for the methicillin-susceptible strains (e.g., ceftriaxone, methicillin-resistant mode MIC of 32 μg/ml; methicillin-susceptible mode MIC of 4 μg/ml). An increase in inoculum resulted in at most a twofold decrease in susceptibility of all strains to FCE 22101.

All the compounds tested, with the exception of moxalactam, showed high activities against *Streptococcus pneumoniae*. One strain showing reduced susceptibility to penicillin (MIC, 0.12 μg/ml) was susceptible to 0.25 μg of FCE 22101 per ml, 0.03 μg of imipenem per ml, and 2 μg of ceftazidime per ml.

In all, five strains of Lancefield group A, 4 strains of Lancefield group B, and 10 strains of Lancefield group D streptococci were tested (not shown in Table 1). The group A streptococci were all susceptible to between 0.06 and 0.12 μg of FCE 22101 per ml. The group B streptococci were susceptible to 0.25 μg or less of FCE 22101 per ml. The group D streptococci were inhibited by between 1 and 4 μg of FCE 22101 per ml and by 0.5 to 1.0 μg of imipenem per ml, but the other cephalosporins (including moxalactam) had no activity (mode MIC, >128 μg/ml).

The 11 β-lactamase-producing strains of *Haemophilus influenzae* were as susceptible to FCE 22101 as were the non-β-lactamase producers. Also included in the strains tested were five which were presumed to have a permeability barrier to ampicillin (i.e., an ampicillin MIC of ≥0.5 μg/ml, with little or no increase in MIC when the inoculum was increased to $10^6$ CFU). These strains were all susceptible to 0.5 to 1 μg of FCE 22101 per ml, whereas they showed a decrease in susceptibility to moxalactam (MIC,

0.5 to 2 μg/ml), ceftiaxone (MIC, 0.04 to 0.06 μg/ml), ceftazidime (MIC, 0.5 to 1 μg/ml), and cefuroxime (MIC, 1 to 16 μg/ml). Imipenem, however, was as active against such strains as against those not having this presumed permeability barrier.

Ceftriaxone was the agent most active against the strains of *Neisseria gonorrhoeae* tested. FCE 22101 was as active as cefuroxime and imipenem, and the 14 β-lactamase-producing strains were as susceptible as the non-β-lactamase-producing strains.

Of the 29 strains of *Bacteroides* spp. tested, 25 were of *B. fragilis*, 2 were of *B. thetaiotaomicron*, and 1 each were of *B. ovatus* and *B. vulgatus*. All were highly susceptible to FCE 22101. One known cefoxitin-resistant (MIC, >64 μg/ml) strain of *B. thetaiotaomicron* was highly resistant to all agents (MIC, ≥128 μg/ml), except to FCE 22101 and imipenem, to which it was susceptible at 0.5 and 8 μg/ml, respectively. The strains of *B. ovatus* and *B. vulgatus* were as susceptible as the other strains to FCE 22101.

In Table 3, the effect of serum on the MICs and MBCs is shown. There was little difference between the MICs and MBCs except for one strain of *Staphylococcus aureus* (methicillin susceptible), when in the absence of serum there was a 32-fold difference, and for one strain of *Proteus mirabilis*, when there was an >8-fold difference. Generally, serum had little effect on the MICs or MBCs. The mean human serum protein binding of FCE 22101 was 40.6% and varied little with the concentration studied (from 40.0% for 5 μg/ml to 35.5% for 200 μg/ml).

## DISCUSSION

FCE 22101, a penem derivative, exhibits a number of differences when compared with other broad-spectrum β-lactams, especially the cephalosporins. Although the drug is somewhat less active against members of the *Enterobacteriaceae* than the recently introduced compounds, the narrow range of susceptibilities to FCE 22101 is noteworthy, since these other agents often show a more marked range of susceptibility (e.g., ceftriaxone, 0.015 to 5 μg/ml). It could therefore be said that FCE 22101 is more predictable in its degree of activity.

FCE 22101 appears to be resistant to the wide range of characterized β-lactamases tested. In particular, it is also active against the clinically important β-lactamase-producing strains of *Haemophilus influenzae* and *Neisseria gonorrhoeae*. In addition to appearing to be resistant to the β-lactamases of the *Bacteroides* spp., it is also extremely active against these strains: the 50% MIC of FCE 22101 being about 16-fold

TABLE 2. Activity of FCE 22101 and other agents against characteristic β-lactamase-producing strains

| Organism | β-Lactamase type | Richmond & Sykes group | MIC (μg/ml) of: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | FCE 22101 | | Ceftriaxone | | Moxalactam | | Imipenem | | Cefuroxime | | Ceftazidime | |
| | | | $10^4$[a] | $10^6$ | $10^4$ | $10^6$ | $10^4$ | $10^6$ | $10^4$ | $10^6$ | $10^4$ | $10^6$ | $10^4$ | $10^6$ |
| *Enterobacter cloacae* | P99+ | I | 2 | 2 | 16 | 32 | 4 | 4 | 0.25 | 0.25 | >128 | >128 | 8 | 16 |
| *Escherichia coli* | D31 | I | 1 | 1 | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.25 | 32 | 64 | 2 | 4 |
| *Escherichia coli* | TEM-1 | III | 0.5 | 0.5 | 0.06 | 0.06 | 0.06 | 0.06 | 0.5 | 0.5 | 4 | 4 | 0.25 | 0.25 |
| *Escherichia coli* | TEM-2 | III | 0.5 | 1 | 0.06 | 0.06 | 0.12 | 0.12 | 0.25 | 0.5 | 2 | 4 | 0.12 | 0.25 |
| *Klebsiella pneumoniae* | SHV-1 | III | 0.5 | 0.5 | 0.03 | 0.03 | 0.06 | 0.06 | 0.25 | 0.25 | 4 | 4 | 0.12 | 0.12 |
| *Klebsiella aerogenes* | K-1+ | IV | 0.5 | 1 | 4 | 16 | 0.06 | 0.06 | 0.25 | 1 | 128 | >128 | 0.12 | 0.12 |
| *Enterobacter cloacae* (1833E) | Broad spectrum | IV | 2 | 2 | 2 | 2 | 0.12 | 0.25 | 0.5 | 0.5 | >128 | >128 | 8 | 16 |
| *Escherichia coli* | OXA-1 | V | 0.5 | 1 | 0.06 | 0.06 | 0.25 | 0.25 | 0.25 | 0.5 | 8 | 8 | 0.12 | 0.25 |
| *Escherichia coli* | OXA-3 | V | 0.5 | 0.5 | 0.03 | 0.03 | 0.06 | 0.06 | 0.25 | 0.5 | 2 | 4 | 0.12 | 0.25 |

[a] Inoculum in CFU per milliliter.

TABLE 3. Effect of increased percentage of human serum on the MICs and MBCs of FCE 22101

| Organism (no. of isolates) | Concn (μg/ml) at indicated human serum level (%) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | | 20 | | 70 | |
| | MIC | MBC | MIC | MBC | MIC | MBC |
| *Escherichia coli* (1) | 1 | 4 | 1 | 2 | 1 | 4 |
| *Escherichia coli* (2) | 1 | 2 | 1 | 2 | 1 | 2 |
| *Klebsiella pneumoniae* (1) | 1 | 2 | 1 | 2 | 1 | 2 |
| *Klebsiella pneumoniae* (2) | 1 | 2 | 1 | 4 | 1 | 2 |
| *Proteus mirabilis* | 2 | ≥16 | 4 | ≥16 | 4 | ≥16 |
| *Proteus mirabilis* | 4 | 8 | 4 | ≥16 | 4 | 4 |
| *Staphylococcus aureus* (1) | 0.06 | 2 | 0.12 | 1 | 0.25 | 1 |
| *Staphylococcus aureus* (2 methicillin resistant) | 0.5 | 2 | 0.5 | 2 | 0.5 | 2 |
| *Streptococcus faecalis* (1) | 2 | 8 | 4 | 4 | 4 | 4 |
| *Streptococcus faecalis* (1) | 4 | 16 | 4 | 8 | 4 | 8 |

lower than that of imipenem (although the 90% MICs were similar) and was about 128-fold lower than that of moxalactam. Of particular interest was the susceptibility of the known cefoxitin-resistant strain of *Bacteroides thetaiotaomicron*. It is not known whether resistance of this strain to the cephalosporins (including moxalactam) is due to a permeability barrier, lack of target site affinity, or β-lactamase hydrolysis; this problem is under further investigation.

FCE 22101, imipenem (10), and the oral penem, Sch 29,494 (1) have similar properties with high activity against *Staphylococcus aureus* and considerable activity against methicillin-resistant strains, a property not shared with the other compounds tested. The relevance of this discovery is difficult to assess until clinical trials have been performed. It can, however, be said that unlike the newer cephalosporins, FCE 22101 should be a potent antistaphylococcal agent. In addition, this compound is active against all gram-positive cocci studied, including *Streptococcus pneumoniae* (unlike moxalactam) and *Streptococcus faecalis*, when the other agents (with the exception of imipenem) were inactive.

FCE 22101 would therefore appear to be less active against many gram-negative pathogenic bacteria than some of the newer cephalosporins, but it has a spectrum of activity which includes the majority of gram-negative and -positive bacteria, a fact that should encourage clinical studies. Another advantage of this compound is the possible development of orally absorbed esters (6). Animal studies show that in mice 47% of the ester FCE 22891 and 32% of FCE 22553 are orally absorbed.

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