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Antibacterial properties of imipenem with special reference to the activity against methicillin-resistant staphylococci, cefotaxime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*

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Imipenem was examined with standardized agar dilution procedures against a wide range of bacteria. Geometric mean MICs against the genera *Escherichia, Klebsiella, Enterobacter, Citrobacter* and *Serratia* were 0·1–0·4 mg/l, and *Proteus* and *Providencia* spp. were inhibited by 0·25–4 mg/l. *Acinetobacter calcoaceticus* var. *anitratum* strains were inhibited by concentrations ranging from 0·12–0·5 mg/l. Methicillin-susceptible staphylococci were highly susceptible to the drug (MICs: $\leq$0·03 mg/l) and enterococci were inhibited by 0·25–16 mg/l. Most of the multi-resistant JK corynebacteria were resistant to imipenem. Imipenem was more active than any other β-lactam against methicillin-resistant staphylococci; this was also demonstrated in a population analysis. Imipenem-resistant minorities in populations, however, were also observed. Cefotaxime-resistant and -intermediate *Enterobacter* and *Citrobacter* strains were inhibited by concentrations of 0·5 mg/l or less. No third-generation cephalosporin nor any other β-lactam showed similarly high activity against these groups of organisms. Among 20 ceftazidime-resistant and 20 ceftazidime-susceptible isolates of *Pseudomonas aeruginosa*, no strain was resistant and only five ceftazidime-resistant strains were intermediately susceptible (MIC, 8 mg/l) to imipenem.

Introduction

The aim of this work was to study the in-vitro activity of imipenem in comparison with other broad-spectrum β-lactam antibiotics against a wide range of bacteria.

Materials and methods

Organisms

The bacterial strains used were recently isolated from clinical specimens and identified according to standard procedures.

Antibiotics

Imipenem (Merck, Sharp & Dohme), ceftazidime (Glaxo), aztreonam (Squibb), cefotaxime (Hoechst), cefpirome (HR810) (Hoechst-Roussel), ceftriaxone (Hoffman La Roche), cefoperazone (Pfizer) and latamoxef (Lilly) were kindly supplied by the manufacturers.

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Table I. In-vitro activity of imipenem and seven β-lactam antibiotics against Enterobacteriaceae

Organisms (no. of strains)	Drug	MIC (mg/l) 50%[a]	90%[a]	Range	Geometric mean
Esch. coli (12)	imipenem	0·12	0·25	≤0·03–0·5	0·11
	ceftazidime	8	16	0·12–16	2·1
	aztreonam	4	8	0·06–8	1·1
	cefpirome	0·06	0·25	≤0·03–1	0·09
	cefotaxime	2	4	0·06–4	0·89
	ceftriaxone	1	1	≤0·03–1	0·40
	cefoperazone	2	16	0·5 –64	2·0
	latamoxef	0·5	1	0·06–1	0·33
Klebsiella spp. (27)	imipenem	0·12	0·25	0·06–1	0·15
	ceftazidime	0·25	0·5	0·06–16	0·23
	aztreonam	8	32	≤0·03–64	1·8
	cefpirome	0·5	2	≤0·03–4	0·36
	cefotaxime	0·5	2	0·06–16	0·38
	ceftriaxone	2	64	≤0·03–128	1·1
	cefoperazone	128	256	0·25–512	38·3
	latamoxef	0·12	1	≤0·03–16	0·14
Enterobacter spp. cefotaxime susceptible (11)	imipenem	0·25	1	0·06–1	0·30
	ceftazidime	1	16	0·25–16	1·6
	aztreonam	0·25	4	≤0·03–16	0·47
	cefpirome	0·25	0·5	≤0·03–0·5	0·22
	cefotaxime	2	8	0·06–8	1·4
	ceftriaxone	4	8	0·06–16	1·5
	cefoperazone	8	8	0·06–16	3·3
	latamoxef	0·5	1	0·06–1	0·34
Enterobacter spp. cefotaxime intermediate/resistant (21)	imipenem	0·25	0·5	≤0·03–0·5	0·20
	ceftazidime	128	256	16–>512	101·6
	aztreonam	32	64	4–128	32·0
	cefpirome	4	8	0·5 –128	2·6
	cefotaxime	128	256	16–>512	115·9
	ceftriaxone	128	512	16–>512	119·8
	cefoperazone	64	256	16–>512	89·0
	latamoxef	8	16	0·5 –128	6·1
C. freundii cefotaxime susceptible (13)	imipenem	0·25	0·25	0·12–1	0·24
	ceftazidime	0·25	4	0·12–4	0·62
	aztreonam	0·25	2	≤0·03–2	0·29
	cefpirome	0·12	0·5	≤0·03–1	0·14
	cefotaxime	1	4	0·06–4	0·85
	ceftriaxone	0·5	8	≤0·03–8	0·56
	cefoperazone	8	16	0·12–64	5·5
	latamoxef	0·06	0·5	0·06–8	0·16
C. freundii cefotaxime intermediate/resistant (17)	imipenem	0·12	0·25	0·12–0·25	0·15
	ceftazidime	128	512	32–512	156·9
	aztreonam	32	128	8–256	39·2
	cefpirome	2	4	0·25–4	1·6
	cefotaxime	64	128	16–128	50·1
	ceftriaxone	64	256	16–256	81·7
	cefoperazone	64	256	32–256	81·7
	latamoxef	2	8	1–32	3·7

Table I—*contd.*

Organisms (no. of strains)	Drug	MIC (mg/l) 50%[a]	90%[a]	Range	Geometric mean
Ser. marcescens (25)	imipenem	0·5	0·5	0·12–1	0·41
	ceftazidime	0·5	2	0·06–16	0·44
	aztreonam	0·5	8	0·06–8	0·74
	cefpirome	0·5	1	⩽0·03–4	0·34
	cefotaxime	8	32	0·12–32	3·1
	ceftriaxone	2	16	0·06–32	1·7
	cefoperazone	64	128	8–128	43·4
	latamoxef	0·25	8	0·12–16	0·76
Proteus and *Providencia* spp.[b] (19)	imipenem	1	2	0·25–4	0·75
	ceftazidime	0·06	0·5	⩽0·03–1	0·05
	aztreonam	⩽0·03	0·03	⩽0·03–0·06	⩽0·03
	cefpirome	0·5	4	0·12–4	0·77
	cefotaxime	⩽0·03	0·06	⩽0·03–0·25	⩽0·03
	ceftriaxone	⩽0·03	0·03	⩽0·03–0·06	⩽0·03
	cefoperazone	⩽0·03	0·03	⩽0·03–0·06	⩽0·03
	latamoxef	0·25	0·5	⩽0·03–0·5	0·17

[a]MIC_{50} and MIC_{90} are the concentrations of antibiotics required to inhibit 50% and 90% of the examined strains, respectively.
[b]*Prot. mirabilis* (6), *Prot. vulgaris* (6), *Prov. rettgeri* (4), *Prov. stuartii* (3).

Methods

Minimal inhibitory concentrations (MICs) were determined according to the NCCLS agar-dilution procedure (National Committee for Clinical Laboratory Standards (NCCLS) (1985)). Mueller–Hinton medium with 3% agar content was used to prevent swarming of *Providencia* and *Proteus* spp. Gonococci (GC) agar base supplemented with 5% defibrinated sheep blood was used for JK corynebacteria.

A population of methicillin-resistant staphylococci was analysed by disaggregation of overnight broth cultures (brief ultrasonication at 20 kHz) and surface inoculation on to drug-containing Mueller-Hinton agar plates with 0·1 ml of appropriate dilutions of the processed broth. Incubation was at 37°C for 48 h. Colony counts served to calculate the number of resistant cells in a population of 10^8 cfu.

Results

The MICs for the Gram-negative and Gram-positive organisms used to define the spectrum of imipenem are presented in Tables I to III. Imipenem was highly active against the Enterobacteriaceae; exceeding the activity of most of the other β-lactam antibiotics tested (Table I). The drug showed less activity against *Proteus* and *Providencia* spp., but MICs were still below the susceptibility threshold of $\leqslant 4$ mg/l. Imipenem was equally active against *Enterobacter* and *Citrobacter* strains resistant or susceptible to cefotaxime. Most of the cefotaxime-resistant strains were also resistant to ceftazidime, aztreonam, ceftriaxone and cefoperazone. Cefpirome and latamoxef

Table II. In-vitro activity of imipenem and seven β-lactam antibiotics against *A. anitratus* and *Ps. aeruginosa*

Organisms (no. of strains)	Drug	MIC (mg/l) 50%	90%	Range	Geometric mean
A. calcoaceticus var. *anitratum* (11)	imipenem	0·25	0·5	0·12–0·5	0·21
	ceftazidime	8	16	4–16	8·5
	aztreonam	32	64	16–64	36·3
	cefpirome	32	64	1–64	20·6
	cefotaxime	16	32	4–32	17·0
	ceftriaxone	16	32	4–32	14·1
	cefoperazone	128	256	128–256	164·7
	latamoxef	16	16	2–32	13·2
Ps. aeruginosa ceftazidime susceptible (20)	imipenem	1	2	0·5–4	1·1
	ceftazidime	2	4	1–8	2·1
	aztreonam	4	16	2–32	5·9
	cefpirome	8	16	2–64	7·7
	cefotaxime	16	64	8–256	26·0
	ceftriaxone	32	128	8–256	29·9
	cefoperazone	8	64	4–128	11·3
	latamoxef	16	32	8–128	16·0
Ps. aeruginosa ceftazidime intermediate/resistant (20)	imipenem	4	8	0·5–8	2·8
	ceftazidime	64	64	16–256	46·9
	aztreonam	64	128	8–128	50·2
	cefpirome	256	512	2–512	119·4
	cefotaxime	512	<512	32–>512	512
	ceftriaxone	>512	>512	32–>512	675·6
	cefoperazone	256	512	8–>512	230·7
	latamoxef	128	256	16–512	152·2

exerted good activity against these problem strains, although the geometric means of their MICs were 10–20 times higher than against cefotaxime-susceptible *Enterobacter* and *Citrobacter* spp.

Imipenem was the most active amongst the agents tested against *Acinetobacter calcoaceticus* var. *anitratum* and *Pseudomonas aeruginosa*, whether susceptible or resistant to ceftazidime (Table II). MICs of imipenem against ceftazidime-resistant *Ps. aeruginosa* were only slightly higher than against susceptible strains. This finding was in sharp contrast to the results obtained with the other β-lactams. The latter all showed highly elevated MICs against the ceftazidime-resistant strains. Cross-resistance was not observed between imipenem and the other drugs examined. Imipenem was highly active against methicillin-susceptible staphylococci (Table III). Compared with the activity against other Gram-positive bacteria (Tischhauser & Kayser, 1983), the drug's activity against enterococci was relatively low. However, 50% of the enterococci were inhibited by 1 mg/l and 90% by 8 mg/l of the drug, respectively. These values were much lower than those of the other β-lactams examined. Antistaphylococcal activity of imipenem was generally superior to that of the other β-lactams tested. Methicillin-resistant staphylococci were inhibited by higher imipenem concentrations than susceptible isolates but only 5% of the strains had MICs above the susceptibility

Table III. In-vitro activity of imipenem and six β-lactam antibiotics against Gram-positive organisms

Organisms (no. of strains)	Drug	MIC (mg/l) 50%	90%	Range	Geometric mean
Staph. aureus methicillin susceptible (19)	imipenem	≤0·03	≤0·03	≤0·03	≤0·03
	ceftazidime	8	16	4–16	8·9
	cefpirome	1	1	0·12–1	0·58
	cefotaxime	2	4	0·5 –4	1·7
	ceftriaxone	4	8	1–8	3·0
	cefoperazone	2	4	1–4	1·9
	latamoxef	16	16	8–16	9·3
Staph. aureus methicillin resistant (19)	imipenem	≤0·03	0·12	≤0·03–64	0·07
	ceftazidime	32	128	4–512	32·0
	cefpirome	2	32	0·5 –64	2·5
	cefotaxime	16	128	1–>512	12·4
	ceftriaxone	16	256	2–>512	17·9
	cefoperazone	16	32	1–>512	15·4
	latamoxef	32	128	8–>512	33·2
Coagulase-negative staphylococcus methicillin susceptible (16)	imipenem	≤0·03	≤0·03	≤0·03	≤0·03
	ceftazidime	8	16	4–16	6·7
	cefpirome	0·25	0·5	0·12–2	0·25
	cefotaxime	1	4	0·5 –8	1·6
	ceftriaxone	2	4	0·5 –8	1·5
	cefoperazone	2	4	0·5 –4	1·5
	latamoxef	16	32	8–32	18·2
Coagulase-negative staphylococcus methicillin resistant (20)	imipenem	0·06	0·5	≤0·03–16	0·09
	ceftazidime	8	32	0·5 –32	8·9
	cefpirome	0·5	4	0·06–16	0·71
	cefotaxime	2	8	0·06–16	2·3
	ceftriaxone	4	32	0·12–32	4·4
	cefoperazone	2	4	0·25–8	2·1
	latamoxef	32	64	8–128	34·3
Enterococci (20)	imipenem	1	8	0·25–16	1·9
	ceftazidime	>512	>512	128–>512	749·6
	cefpirome	16	512	1–>512	34·3
	cefotaxime	256	512	32–>512	294·1
	ceftriaxone	128	512	4–>512	123·6
	cefoperazone	64	512	8–512	64·0
	latamoxef	>512	>512	128–>512	861·1
Multiresistant JK corynebacteria (14)	imipenem	256	512	0·5 –>512	115·9
	ceftazidime	>512	>512	128–>512	655·8
	cefpirome	512	>512	4–>512	141·3
	cefotaxime	>512	>512	8–>512	269·0
	ceftriaxone	>512	>512	8–>512	243·6
	cefoperazone	>512	>512	16–>512	231·9
	latamoxef	>512	>512	256–>512	760·8

breakpoint of 4 mg/l. Figure 1 shows the population analysis of the pencillinase-negative *Staphylococcus aureus* strain FK 362 with respect to imipenem, penicillin G and methicillin. Although heterogeneity was also found with imipenem, the population was more susceptible to imipenem than to penicillin G and to methicillin.

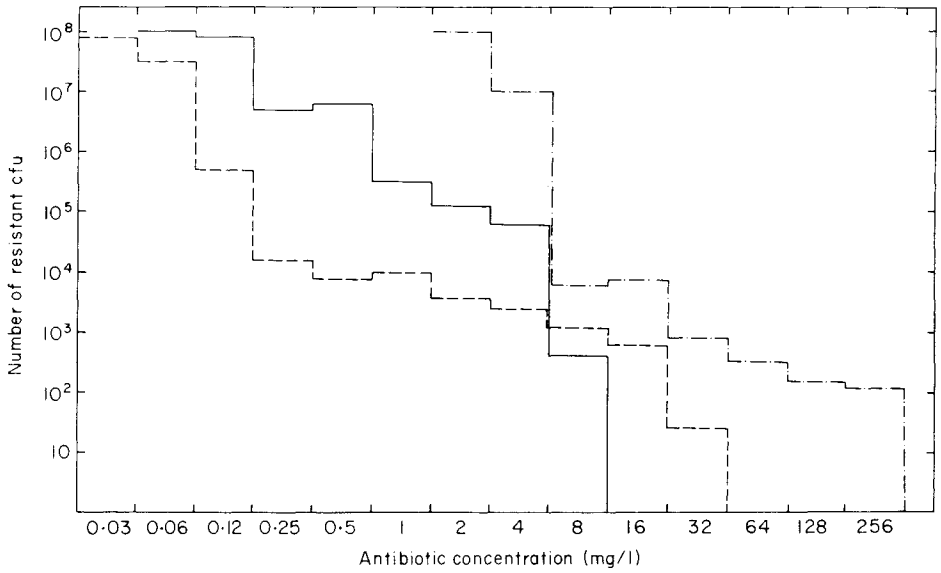

Figure 1. Number of viable units resistant to each concentration of antimicrobial agent remaining after plating an inoculum of 10^8 cfu of methicillin-resistant, β-lactamase-negative *Staph. aureus* strain FK 362 and incubating at 37°C for 48 h (– – – imipenem; —— penicillin G; —·—·— methicillin).

Discussion

An outstanding property of imipenem is its activity against strains of Enterobacteriaceae resistant to third-generation cephalosporins. This property may be due to the stability of imipenem to the chromosomal cephalosporinase responsible for resistance in these organisms (Livermore, Williams & Williams, 1981; Seeberg, Tolxdorff-Neutzling & Wiedemann, 1983) as well as its high penetrability through the outer membrane of Gram-negative bacteria due to its zwitterionic character and compact molecular structure (Yoshimura & Nikaido, 1985). Stability to β-lactamases and good penetrability of the cell wall also could explain the activity of imipenem against ceftazidime-resistant *Ps. aeruginosa.*

Another outstanding feature of imipenem is its activity against Gram-positive cocci including the enterococci. The majority of the methicillin-resistant staphylococci were susceptible to imipenem in standard agar dilution tests, but with an inoculum of 10^4 cells per spot and incubation for 20 h at 35°C, these tests were unfavourable for the expression of intrinsic resistance to β-lactam antibiotics in staphylococci. The majority of cells in a population of methicillin-resistant *Staph. aureus* will be susceptible to imipenem, but minorities of a few more or less resistant cells may occur. Despite this situation, imipenem seems to be an effective agent in the treatment of infections caused by methicillin-resistant staphylococci (Fan *et al.*, 1986).

Thus, imipenem presents an impressive potential in the therapy of bacterial infections.

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