

ACTIVITY OF IMPENEM AGAINST CLINICAL ISOLATES

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Summary

Imipenem is a new carbapenem antibiotic which is highly active against both Gram positive and Gram negative bacteria. The purpose of this study is to establish the *in-vitro* activity of imipenem against recent clinical isolates of bacteria obtained from patients at the Kuala Lumpur General Hospital. Minimum inhibitory concentrations of the antibiotic against these isolates were determined using an agar dilution method. With the exception of *Flavobacterium* sp, some *Pseudomonas* sp and certain other non-fermentative Gram negative bacilli, imipenem was found to be active against a wide range of both Gram positive and Gram negative organisms. Imipenem could be a valuable alternative in cases of hospital infection caused by multiply resistant organisms.

Keywords: Imipenem, carbapenem, antibiotic sensitivity testing.

INTRODUCTION

Imipenem is a new antibiotic of the carbapenem group. Carbapenems are naturally occurring beta-lactam compounds. The first carbapenem, thienamycin, was isolated from *Streptomyces cattleya* in 1976. This compound was however rather unstable and therefore clinically not useful. Imipenem is the stabilised N-formimidoyl derivative of thienamycin. The carbapenems are characterised by their broad spectrum activity, high degree of resistance to hydrolysis by beta-lactamases and their susceptibility to the renal enzyme, dehydropeptidase-I. For this last reason imipenem is combined with cilastin sodium, an inhibitor of dehydropeptidase-I. Cilastin sodium has no antibacterial activity. Recently, imipenem-cilastin was approved for clinical use in Malaysia. The purpose of this study therefore was to establish the *in-vitro* activity of imipenem against local clinical isolates of bacteria.

MATERIALS AND METHODS

A total of 533 recent clinical isolates were obtained from patients at the Kuala Lumpur General Hospital over a six month period between 1st January 1988 and 30th June 1988. They comprised 335 strains of *Enterobacteriaceae*, 166 strains of non-fermentative Gram negative bacilli and 32 strains of *Staphylococcus aureus*. The details of the breakdown by species is shown in Table 1.

An agar dilution method was used to determine minimum inhibitory concentrations of imipenem against the clinical isolates. The medium used was Diagnostic Sensitivity Test

Agar (Oxoid) for all strains except for *Pseudomonas aeruginosa* where Mueller-Hinton agar (BBL) was used. Overnight broth cultures of the test organisms were diluted a hundred fold to serve as the inocula and plates were inoculated with the inocula using a Denley multipoint inoculator. Each inoculating pin delivered approximately 1.5 microlitres of the inoculum. After inoculation the plates were incubated at 37°C for 18 hours before being read. The minimum inhibitory concentration (MIC) was defined as the minimum concentration of antibiotic that inhibits all visible growth of bacteria on the plate. The MIC of gentamicin against the Gram negative organisms and the MIC of methicillin against the *Staphylococcus aureus* strains were similarly established. The incubation temperature employed with methicillin testing was 30°C.

RESULTS

The results are expressed as the MIC range, MIC₅₀ and the MIC₉₀ (Table 1). The MIC₅₀ and the MIC₉₀ are the concentrations of the antibiotic that inhibit 50% and 90% of the strains tested respectively. The *Enterobacteriaceae* were in general very susceptible to imipenem with the exception of *Proteus* sp and *Morganella* sp where the MIC₉₀s were 4.0 mg/l and 8.0 mg/l respectively. Nevertheless all *Enterobacteriaceae* strains were inhibited by a concentration of 8 mg/l. Similarly all the *Acinetobacter calcoaceticus* and *Pseudomonas aeruginosa* strains that were tested were found to be inhibited by an

TABLE 1
SUSCEPTIBILITY OF 533 CLINICAL ISOLATES TO IMPENEM

Organism (No. of strains)	Range	MIC ₅₀	MIC ₉₀
		(all values in mg/l)	
<i>E. coli</i> (86)	<0.25–4.0	<0.25	0.5
<i>Enterobacter cloacae</i> (49)	<0.25–4.0	1.0	2.0
<i>Klebsiella pneumoniae</i> (70)	<0.25–2.0	0.5	2.0
<i>Serratia marcescens</i> (2)	0.5–1.0	0.5	1.0
<i>Salmonella sp</i> (54)	<0.25–1.0	0.5	1.0
<i>Salmonella typhi</i> (10)	<0.25–0.5	<0.25	<0.25
<i>Salmonella paratyphi</i> (4)	<0.25–0.5	0.5	0.5
<i>Proteus mirabilis</i> (37)	2.0–8.0	4.0	4.0
<i>Morganella morganii</i> (13)	2.0–8.0	4.0	8.0
<i>Proteus vulgaris</i> (4)	–	4.0	4.0
<i>Proteus rettgeri</i> (3)	1.0–4.0	2.0	4.0
<i>Citrobacter diversus</i> (3)	–	<0.25	<0.25
<i>Pseudomonas aeruginosa</i> (84)	<0.25–8.0	1.0	2.0
<i>Pseudomonas sp</i> (25)*	0.25–>32.0	2.0	>32.0
<i>Flavobacterium meningosepticum</i> (10)	<0.25–>32.0	32.0	>32.0
<i>Flavobacterium sp</i> (5)	4.0–>32.0	8.0	>32.0
<i>Alcaligenes odoratum</i> (8)	2.0–>32.0	2.0	>32.0
<i>Acinetobacter sp</i> (27)	<0.25–2.0	0.5	2.0
<i>Achromobacter xylosoxidans</i> (7)	2.0–16.0	2.0	16.0
<i>Staphylococcus aureus</i> (32)	<0.25–32	<0.25	16.0

* The 25 strains of *Pseudomonas sp* comprised of *Ps. mallei* (8 strains), *Ps. maltophilia* (7), *Ps. cepacia* (3), *Ps. acidovorans* (2) and one strain each of *Ps. pseudomallei*, *Ps. testosteronii*, *Ps. putida*, *Ps. fluorescens* and *Ps. paucimobilis*.

TABLE 2
SUSCEPTIBILITY OF 198 GENTAMICIN-RESISTANT GRAM NEGATIVE BACILLI TOWARDS IMPENEM

Organism (No. of strains)	No. (%) inhibited by imipenem at 8 mg/l
<i>E. coli</i> (19)	19 (100%)
<i>Enterobacter cloacae</i> (20)	20 (100%)
<i>Klebsiella pneumoniae</i> (39)	39 (100%)
<i>Salmonella sp</i> (9)	9 (100%)
<i>Proteus mirabilis</i> (13)	13 (100%)
<i>Morganella morganii</i> (3)	3 (100%)
<i>Proteus sp</i> (5)	5 (100%)
<i>Pseudomonas aeruginosa</i> (31)	31 (100%)
<i>Pseudomonas sp</i> (22)	13 (50%)
<i>Flavobacterium sp</i> (11)	2 (18%)
<i>Alcaligenes sp</i> (6)	4 (66%)
<i>Acinetobacter calcoaceticus</i> (14)	14 (100%)
<i>Achromobacter xylosoxidans</i> (6)	3 (50%)
All strains (198)	175 (88.4%)

imipenem concentration of 8 mg/l. Its activity against other *Pseudomonas* sp was variable. The majority of *Pseudomonas maltophilia* and *Pseudomonas cepacia* strains had imipenem MICs of > 8 mg/l. In contrast 7 out of the 8 *Pseudomonas mallei* strains were inhibited at 8 mg/l as were the two strains of *Pseudomonas acidovorans* and the single isolates of *Pseudomonas pseudomallei*, *Pseudomonas testosteronii*, *Pseudomonas putida*, *Pseudomonas fluorescens* and *Pseudomonas paucimobilis*. The *Flavobacterium* strains had an MIC₅₀ and MIC₉₀ of 16 mg/l and > 32 mg/l respectively. Of the 10 strains of *Flavobacterium meningosepticum* tested 4 were inhibited at 8 mg/l. The activity of imipenem against *Alcaligenes odoratum* and *Achromobacter xylosoxidans* strains was again variable. Six out of the 8 *Alcaligenes odoratum* strains and 4 out of the 7 *Achromobacter xylosoxidans* strains were inhibited by 8 mg/l of imipenem.

Of the 32 strains of *Staphylococcus aureus*, 16 were methicillin-resistant or MRSA (MIC methicillin > 2 mg/l). Eleven of the 16 MRSA strains were inhibited by imipenem at 8 mg/l. The geometric mean imipenem MIC for the 16 MRSA was 2.93 mg/l in contrast to a corresponding geometric mean of 0.27 mg/l for the methicillin sensitive (MSSA) strains.

Table 2 shows the susceptibility of the gentamicin resistant Gram negative bacilli towards imipenem. Of the 501 Gram negative bacilli in this study, 198 or 30.5% had gentamicin MICs of >2 mg/l. All the gentamicin resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus* strains were inhibited by 8 mg/l of imipenem.

DISCUSSION

It has been shown that administration of 500 mg of imipenem gives blood levels that exceed 4 mg/l for 2.5 – 3.0 hours. Based on these pharmacokinetic characteristics the MIC breakpoints which have been suggested for imipenem are >8.0 mg/l for the resistant category, 8.0 mg/l for the moderately sensitive and <4.0 mg/l for the sensitive category.² The majority of the local strains of *Enterobacteriaceae* were highly susceptible with the exception of *Proteus* and *Morganella*. Of the 335 strains of *Enterobacteriaceae* tested, 253 strains or 75.5% were inhibited by imipenem at a concentration of 4 mg/l. The 7 strains of *Enterobacteriaceae* that had imipenem MIC's of 8.0 mg/l comprised 5 strains of *Proteus mirabilis* and 2 strains of *Morganella morganii*. Nevertheless based on the

MIC breakpoints suggested, all the *Enterobacteriaceae* that were tested could be regarded as sensitive or moderately sensitive. Imipenem also showed good activity against *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus*. All the strains tested were found to be sensitive. This pattern of susceptibility to imipenem among the local clinical isolates as well as the resistance encountered with *Pseudomonas maltophilia* and *Pseudomonas cepacia* has been previously described.³ It is interesting to note that the other *Pseudomonas* sp in this study were susceptible but the numbers are far too small to come to any general conclusion. We found imipenem to have activity against some strains of *Flavobacterium meningosepticum*, a not uncommon cause of neonatal meningitis in Malaysia.⁴ It may be worthwhile testing for susceptibility to imipenem in cases of flavobacterium meningitis, a condition which is often rather difficult to treat.

The role of imipenem in the treatment of MRSA infections has been studied by several workers. Though imipenem is very active against methicillin-sensitive *Staphylococcus aureus* (MSSA), imipenem has been found to induce resistance in MRSA.⁵ There is also a wide disparity in imipenem MICs between MRSA and MSSAs. Despite this imipenem has been shown to be an effective agent in the treatment of both MRSA and MSSA infections.⁶ Further clinical trials will however have to be done to establish its place in the treatment of MRSA infections. This would be of particular importance in our country since the incidence of MRSA in many of our hospitals is significantly high.⁷

Infections caused by multiply resistant Gram negative bacilli is a major problem in our hospital. Gentamicin resistance as shown in this study is particularly prevalent. Since imipenem is active against many of these gentamicin resistant organisms, in particular *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter calcoaceticus*, it would be a useful alternative in the treatment of such hospital acquired infections.

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