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Biapenem

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Contents

Abstract

▲ Biapenem is a new parenteral carbapenem antibacterial agent with a broad spectrum of *in vitro* antibacterial activity encompassing many Gram-negative and Gram-positive aerobic and anaerobic bacteria, including species producing β-lactamases.

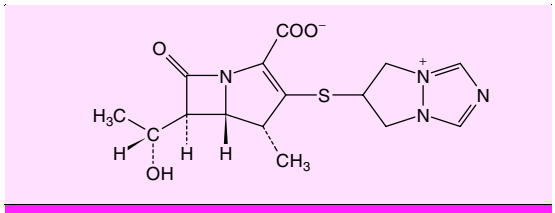
▲ Biapenem is more stable than imipenem, meropenem and panipenem to hydrolysis by human renal dihydropeptidase-I (DHP-I), and therefore does not require the coadministration of a DHP-I inhibitor.

▲ After intravenous administration, biapenem is widely distributed and penetrates well into various tissues (e.g. lung tissue) and body fluids (e.g. sputum, pleural effusion, abdominal cavity fluid).

▲ In randomised, nonblind or double-blind clinical trials, biapenem showed good clinical and bacteriological efficacy (similar to that of imipenem/cilastatin) in the treatment of adult patients with intra-abdominal infections, lower respiratory infections or complicated urinary tract infections.

▲ Biapenem is generally well tolerated. The most common adverse events in clinical trials were skin eruptions/rashes, nausea and diarrhoea.

Features and properties of biapenem	
Indications	
Treatment of bacterial infections	Launched in March 2002 in Japan; Phase II in the US
Antibacterial class	
Carbapenem	
Mechanism of action	
Inhibition of bacterial cell wall synthesis	
Dosage and administration	
Usual dosage in clinical trials in Japan	300mg twice daily
Dosage in clinical trial in Sweden	500mg three times daily
Route of administration	Intravenous (by infusion over 30 to 60 minutes)
Pharmacokinetic profile (300mg single intravenous infusion in healthy adult volunteers)	
Maximum plasma concentration	17.35 mg/L
Area under the plasma concentration-time curve	29.24 mg • h/L
Elimination half-life	1.03h
Renal clearance	6.63 L/h
Adverse events	
Most frequent	Skin eruptions/rashes, nausea, diarrhoea, eosinophilia, ↑ ALT/AST levels



Biapenem

The carbapenems, such as biapenem, imipenem and meropenem, have the broadest spectra of antibacterial activity of all the β-lactams and provide excellent coverage of many Gram-negative and Gram-positive aerobic bacteria, and anaerobic bacteria. These agents, which inhibit bacterial cell wall synthesis, show fewer common resistance problems than other β-lactams, largely because of their stability to hydrolysis by many β-lactamases (e.g. chromosomal and plasmid-mediated β-lactamases, including extended-spectrum enzymes) coupled with their ability to bind strongly to essential penicillin-binding proteins and to penetrate well into Gram-negative bacteria.[1-6]

The early carbapenems (e.g. imipenem) are not stable to hydrolysis by human renal dihydropeptidase-I (DHP-I) and therefore are coadministered with a DHP-I inhibitor (e.g. cilastatin). Biapenem is a newer parenteral carbapenem which, unlike imipenem, has a 1β-methyl group at the C1 position conferring stability to hydrolysis by human renal DHP-I.[7-9] In *in vitro* investigations, biapenem was more stable to hydrolysis by human renal DHP-I than imipenem, meropenem and panipenem.[7] Biapenem is therefore administered as a single agent without a DHP-I inhibitor.

Some β-lactams, including penicillin and imipenem, occasionally cause convulsions/seizures in humans and animals.[10,11] However, biapenem appeared to have weaker convulsant activity than imipenem, panipenem and cefazolin in *in vitro* and *in vivo* investigations.[12] Biapenem did not induce severe convulsions or show neurotoxic potential in rats[11] and showed a substantially lower potential than imipenem for evoking convulsions in mice.[10,12] These beneficial features of biapenem were attributed to the presence of a methyl group at the 1β position and a triazolium radical on the side chain at position 2 of the molecule,[11] and to a lower potential for biapenem to inhibit gamma aminobutyric acid receptor binding than imipenem.[10,12]

1. Antibacterial Activity

In Vitro Activity

The *in vitro* activity of biapenem against a broad range of pathogens has been investigated in a large number of studies conducted in Japan, North America and Europe. In this section, *in vitro* activity refers to the minimum inhibitory concentrations (MIC) for a given agent determined by use of broth or agar dilution techniques and a bacterial inoculum size of 10^4 to 10^6 colony forming units (cfu). MIC_{50} and MIC_{90} values are the minimum concentrations inhibiting 50 and 90% of bacterial strains, respectively.

National Committee for Clinical Laboratory Standards (NCCLS) breakpoint concentrations for biapenem have not yet been established. However, biapenem breakpoint concentrations of ≤4 and >8mg/L for susceptible and nonsusceptible aerobic bacteria, respectively, have been suggested and were used in the largest *in vitro* study conducted to date.[13] Interpretive breakpoints for comparator drugs discussed in this section are based on NCCLS criteria.

Results of *in vitro* investigations indicate that the antibacterial activity profile of biapenem has not changed appreciably during the last 10 years, with little or no evidence of the emergence of resistance over time.[5,13-16]

Biapenem has a broad spectrum of antibacterial activity encompassing many Gram-negative and Gram-positive aerobic, and anaerobic bacteria, including species producing β-lactamases. Percentages of Gram-negative and Gram-positive pathogens susceptible to biapenem and two other carbapenems (imipenem and meropenem) in a large worldwide study[13] (n = >6000 clinical iso-

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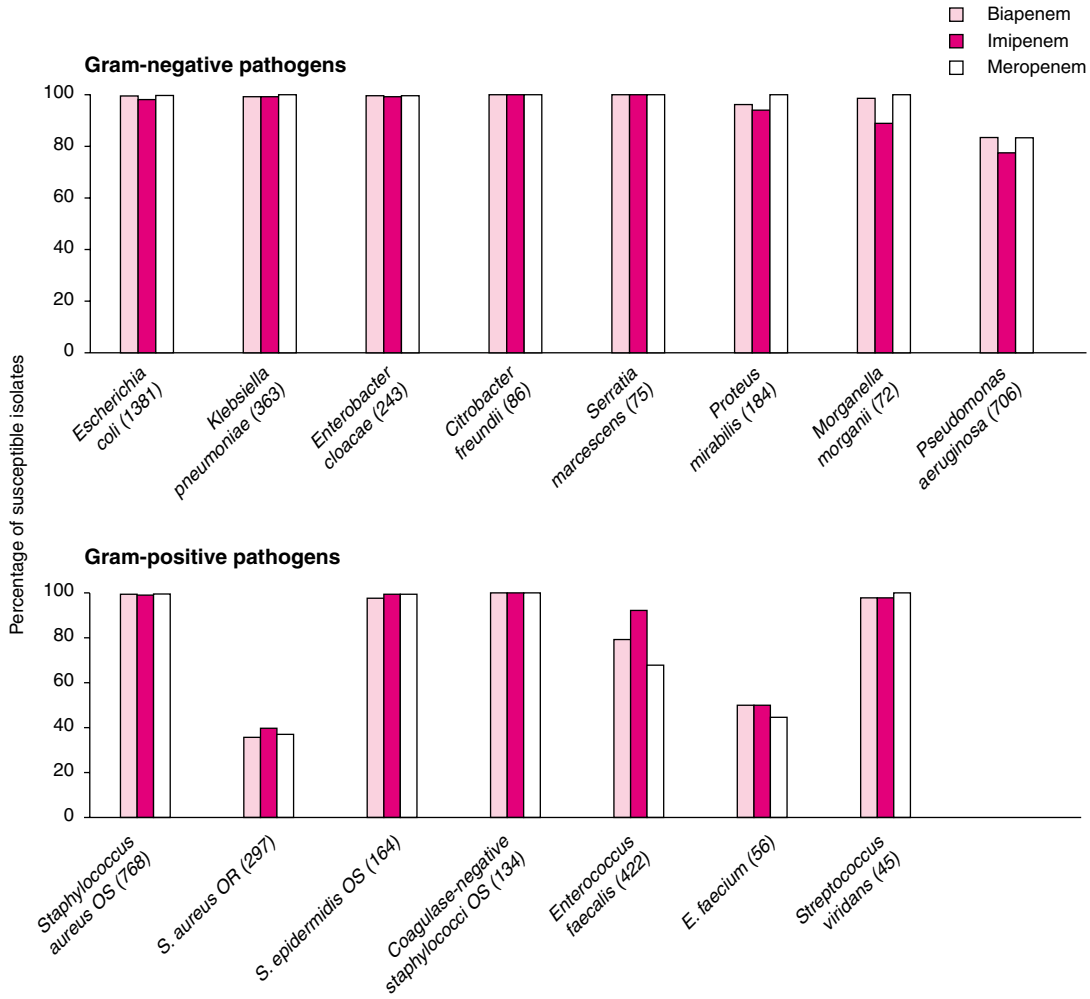

Fig. 1. *In vitro* activity of biapenem, imipenem and meropenem against Gram-negative (top) and Gram-positive pathogens (bottom) in a large (n = >6000 clinical isolates) worldwide study.[13] Percentages of Gram-negative or Gram-positive bacteria susceptible to biapenem, imipenem or meropenem at concentrations of ≤4 mg/L. Numbers in parentheses indicate the number of strains tested. **OR** = oxacillin-resistant; **OS** = oxacillin-susceptible.

lates) are shown in figure 1. Bacterial isolates were collected from Japan, the USA, Canada, Brazil, Switzerland and Spain.

Gram-Negative Aerobic Bacteria

• Biapenem showed good *in vitro* activity against a wide range of Gram-negative bacteria in numerous studies (n = >100 clinical isolates in most studies).[4,13-15,17-24] In general, the *in vitro* activity of biapenem was broadly similar to that of both imipenem and meropenem, although it showed better activity against some Gram-negative pathogens than imipenem in several studies.[4,19,24,25] The *in vitro* activity of biapenem, compared with that of imipenem and meropenem, against a range of clinically isolated strains (n = 850) of Gram-negative pathogens in a recent Japanese study is shown in figure 2.[17]

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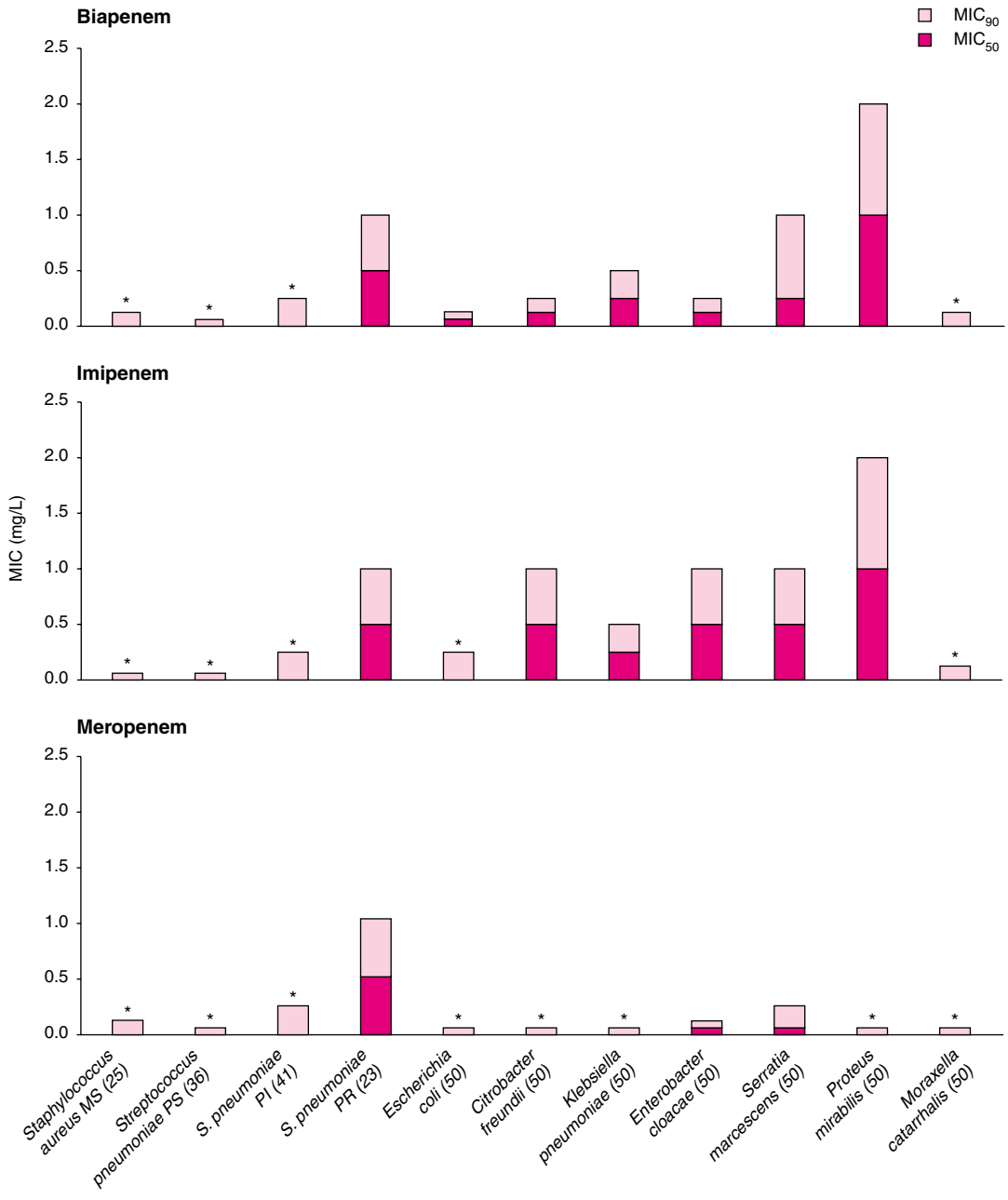

Fig. 2. *In vitro* activity of biapenem, imipenem and meropenem against 850 strains of Gram-negative and Gram-positive pathogens isolated from January 1998 to September 2000 in a study conducted in Japan.[17] Numbers in parentheses indicate the number of strains tested. **MIC**$_{50}$ and **MIC**$_{90}$ = minimum concentrations required to inhibit 50 and 90% of strains; **MS** = methicillin-susceptible; **PI** = penicillin-intermediate; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; * indicates MIC$_{50}$ values are the same as MIC$_{90}$ values.

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• *Escherichia coli* (MIC_{90} range 0.03 to 0.12 mg/L[13-15,17-20,26]), *Klebsiella pneumoniae* (MIC_{90} range 0.12 to 0.78 mg/L[13-15,17,20,26]), *Morganella morganii* (MIC_{90} 1.56[20] and 2 mg/L[19,21]), *Proteus mirabilis* (MIC_{90} range 0.39 to 3.13 mg/L[13,17-21,26]) and *Citrobacter freundii* (MIC_{90} range 0.12 to 0.78 mg/L[13,14,17,19-21,26]) were among the Enterobacteriaceae highly susceptible to biapenem at concentrations usually well below 4 mg/L in studies performed in several countries. Importantly, the spectrum of activity of biapenem also included those Enterobacteriaceae which produced extended-spectrum β-lactamases.[22,27,28] On the basis of results of many *in vitro* investigations, biapenem is considered to be more active than imipenem against most Enterobacteriaceae.[9] However, biapenem showed variable activity against *Serratia marcescens* (MIC_{90} range 0.5 to 8 mg/L[14,15,17,19,21]) and was essentially inactive against *Providencia rettgeri* (MIC_{90} > 8mg/L[13]).

• The common respiratory tract pathogen *Moraxella catarrhalis* was highly susceptible to biapenem in several investigations (MIC_{90} range ≤0.06 to 0.12 mg/L[6,17,18,23,29]). In addition, biapenem showed variable activity against *Haemophilus influenzae* (MIC_{90} range 1 to 8 mg/L[14,15,17-21,23,26,29]).

• During the last decade, there has been a steady increase in the incidence of *Pseudomonas aeruginosa* resistant to β-lactam antibacterials, including carbapenems, in Japan[30,31] and other countries.[32] Nevertheless, during this time, biapenem has generally shown moderate or good *in vitro* activity against imipenem-susceptible clinical (usually nosocomial) *P. aeruginosa* isolates, with reported MIC_{90} values ranging from 1.5 to 16 mg/L (median 8 mg/L).[4,6,13,17,19,24,25,32-35] Comparisons of biapenem, imipenem, meropenem and panipenem MIC_{90} values against strains of *P. aeruginosa* (from January 1994 to December 1996) showed a tendency towards less resistance to biapenem than to the other carbapenems over time.[31] Unlike the other carbapenems, biapenem MIC_{90} values against *P. aeruginosa* (inoculum size 10^8 cfu/ml) did not change from 1994 to 1996. The biapenem MIC_{90} was 12.5 mg/L.[31]

• Strains of *P. aeruginosa* resistant to ceftazidime or ofloxacin were susceptible to biapenem, as were strains producing β-lactamases.[24,32,34,35]

• In a large global study of 706 clinical isolates of *P. aeruginosa* reported in 1993 (figure 1), 83.4% were susceptible to biapenem at a concentration of ≤4 mg/L: MIC_{50} and MIC_{90} values were 0.5 and >8 mg/L, respectively, and 77.5 and 83.3% of isolates were susceptible to imipenem and meropenem at concentrations of ≤4 mg/L.[13]

• Although the *in vitro* activity of biapenem against *P. aeruginosa* tended to be similar to that of imipenem in most investigations, biapenem was more active than imipenem in several studies.[4,19,24,25] For example, of 67 clinical isolates of *P. aeruginosa*, 98% were susceptible to biapenem at concentrations of ≤8 mg/L, compared with 84% susceptible to imipenem (at concentrations ≤8 mg/L) in a New Zealand study; MIC_{90} values were 4 mg/L for biapenem and 8 mg/L for imipenem.[25] Biapenem was 2-fold more active than imipenem against clinical isolates of *P. aeruginosa* from Italy (MIC_{90} values were 8 and 16 mg/L[19]) and from Japan.[4,24]

• More recently, an *in vitro* study of drug activity against 288 clinical isolates of *P. aeruginosa* from hospitalised patients in Japan reported MIC_{90} values of 16, 16, 8 and 32 mg/L for biapenem, imipenem, meropenem and panipenem, respectively; corresponding MIC_{50} values were 1, 2, 1 and 8 mg/L. Against ceftazidime-resistant (MIC ≥16 mg/L) strains of *P. aeruginosa* (n = 75), biapenem, imipenem, meropenem and panipenem MIC_{90} values were 8, 8, 8 and 16 mg/L, respectively.[34] A subsequent investigation of 106 Japanese clinical isolates of *P. aeruginosa* produced results that differed slightly from the earlier study; MIC_{90} values for biapenem, imipenem, meropenem and panipenem were 16, 32, 8 and 32 mg/L, respectively.[6]

• Like *P. aeruginosa*, *Acinetobacter baumannii* is an important nosocomial Gram-negative pathogen, especially in the intensive care unit setting.[36]

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Biapenem displayed excellent *in vitro* activity against clinical isolates of *A. baumannii* obtained worldwide[13] and from hospitalised patients in Canada.[36] MIC_{50} and MIC_{90}values for biapenem were both 0.5 mg/L, compared with 0.5 and 1.0 mg/L, respectively, for imipenem. None of the 149 isolates tested were resistant to biapenem or imipenem.[36]

Gram-Positive Aerobic Bacteria

- Biapenem demonstrated good or excellent antibacterial activity against numerous Gram-positive pathogens (n >100 clinical isolates in most studies)[13-16,18-21,23-26,29,37,38] (figures 1 and 2) with many species susceptible to concentrations of ≤4 mg/L (figure. 1).[13]
- Biapenem exhibited very good activity against clinical isolates of *Streptococcus pneumoniae* (penicillin susceptibility was often not reported) obtained from patients in various geographical areas, including Japan, Canada and the US; MIC_{90} values ranged from ≤0.06 to 0.5 mg/L.[14,15,26,39,40] The biapenem breakpoint concentration for pneumococcal pneumonia (recommended by the Japanese Society of Chemotherapy) is 2 mg/L.[41]
- Of note, penicillin-susceptible (n = 49), -intermediate (n = 77) and -resistant (n = 51) strains of *S. pneumoniae* were all highly susceptible to biapenem in a US study.[38] All tested penicillin-susceptible strains of *S. pneumoniae* were susceptible to biapenem at a concentration of 0.03 mg/L, and all penicillin-intermediate and penicillin-resistant strains were susceptible to biapenem 0.25 mg/L. In the same study, both imipenem and meropenem also showed good activity, similar to that of biapenem, against penicillin-susceptible, -intermediate and -resistant pneumococci.[38]
- In a recent Japanese investigation, biapenem showed good activity against *S. pneumoniae* (51 penicillin-susceptible strains; 71 penicillin-intermediate strains; 78 penicillin-resistant strains) isolated from patients with respiratory tract infections. Biapenem MIC_{50} and MIC_{90} values against all strains were 0.25 and 0.5 mg/L, respectively.[40] *S. pyogenes* strains were also highly susceptible to biapenem in several other studies (MIC_{90} range <0.006 to 0.03 mg/L[20,25,26,37]).
- In addition, biapenem was active against methicillin-susceptible *Staphylococcus aureus* (MIC_{90} range 0.06 to 0.5 mg/L[13-15,19,23,25,26,37]), *S. epidermidis* (MIC_{90} values were 0.12[18] and 1 mg/L[13]) and methicillin-susceptible coagulase-negative streptococci (MIC_{90} range 0.5 to 2 mg/L[13,19,37]). In general, biapenem was at least as active as imipenem against Gram-positive bacteria, although imipenem showed a trend towards slightly better activity than biapenem against some Gram-positive pathogens in some studies.[4,23-25,37]
- Like imipenem and meropenem, biapenem usually showed only moderate activity against *Enterococcus faecalis*, with MIC_{90} values ranging from 3.1 to 16 mg/L.[13-15,17,19-21,37] In common with imipenem, meropenem and panipenem, biapenem was essentially inactive against methicillin-resistant *S. aureus* (MIC_{90} values ranged from 32 to 128 mg/L[14,15,17,20,21,23,26]) and *E. faecium* (MIC_{90} values were usually >128 mg/L[18,19,21]).

Anaerobic Bacteria

- Biapenem displayed excellent activity against a wide range of clinical isolates (usually >150 isolates/study) of Gram-negative (e.g. *Bacteriodes* spp., *Prevotella* spp.) and Gram-positive (e.g. peptostreptococci, clostridia) anaerobes, including β-lactamase-producing strains.[14,15,17,20,39,42-46] The antibacterial activity of biapenem was generally similar to that of imipenem against all species of anaerobes tested.
- In the largest of these studies (n = 539 isolates),[45] 100% of all tested strains of *Bacteriodes fragilis*, *Prevotella* spp. *Fusobacterium* spp. *Clostridium* spp. and *Peptostreptococcus* spp. were susceptible to biapenem at a concentration of 8 mg/L. In another study, biapenem was 32-fold more active than clindamycin and 4-fold more active than metronidazole against all tested anaerobes.[42]

Bactericidal Effects

- Biapenem exhibited a marked and early stationary-phase bactericidal effect against clinically relevant bacteria (e.g. *P. aeruginosa*, *S. aureus*, *E. coli* and *K. pneumoniae*) in a number of stud-

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ies.[6,35,47,48] The bactericidal activity of biapenem was augmented by the presence of 10% fresh human serum in the agar medium, and the rod-shaped *P. aeruginosa* bacteria became spheroblasts or bulge forms, indicating marked cell surface damage, upon bacteriolysis.[6]

- Biapenem exerted a greater bactericidal effect than some other carbapenems against *P. aeruginosa*,[48] including some typically resistant, adherent biofilm-forming strains,[47] and several efflux system mutants.[49] Of five tested agents (biapenem, imipenem, meropenem, panipenem and ceftazidime), only biapenem showed bactericidal activity against *P. aeruginosa* KG5007, a mutant strain overexpressing *MexCD-OprJ*.[49]

- The *in vitro* activity of biapenem against *P. aeruginosa* was retained in the presence of bacterial inocula 10 times higher than usual inocula sizes. The excretory system of resistant *P. aeruginosa* had little effect on biapenem, thereby affording the drug good permeability into various strains of the pathogen.[35]

- The bactericidal activity of biapenem against two penicillin-resistant strains of *S. pneumoniae* isolated from patients with respiratory tract infections in Japan was greater than that of cefotaxime and cefotiam in a recent investigation.[40] At a biapenem concentration of 0.25 mg/L, concentrations of viable cells for both of the penicillin-resistant strains of *S. pneumoniae* had decreased from about 7 $\log_{10}$ cells/ml at baseline to <2 $\log_{10}$ cells/ml after incubation for 6 hours. In contrast, at concentrations of 1 mg/L for cefotaxime and 4 mg/L for cefotiam, viable cell counts had decreased to almost 4 and about 3 $\log_{10}$ cells/ml at 6 hours.[40]

Postantibiotic Effects

- In contrast to many other β-lactam agents, but in common with imipenem, biapenem has shown a marked postantibiotic effect (i.e. suppression of bacterial growth after drug concentrations have decreased to below the MIC for a particular pathogen) against Gram-negative and Gram-positive bacteria.[6,50,51] The postantibiotic effect of biapenem against *P. aeruginosa* was augmented in the presence of fresh human plasma. Delayed bacterial regrowth after biapenem exposure was reported with *E. faecalis*[51] and *P. aeruginosa*.[6,50]

2. Pharmacokinetic Properties

The pharmacokinetic properties of biapenem, administered as single or multiple doses, have been investigated in healthy adult volunteers,[52,53] individuals with renal impairment[54] and elderly volunteers.[55] Data reviewed in this section are reported in fully published papers, abstracts and the manufacturer's prescribing information.[56] All but one[57] of the studies reviewed here enrolled Japanese volunteers. Biapenem was administered as an intravenous infusion over 30 or 60 minutes in all of the investigations.

Plasma Drug Concentrations

- Biapenem had an almost linear pharmacokinetic profile in healthy male volunteers who received single 20 to 600mg doses (n = 22) or multiple 300 or 600mg doses twice daily for several days (n = 10).[52] Mean maximum plasma biapenem concentrations (C_{max}) values were 1.05, 2.41, 4.35, 8.78, 17.35 and 32.41 mg/L, respectively, after single doses of 20 (n = 2), 40 (n = 2), 80 (n = 3), 150 (n = 5), 300 (n = 5) or 600mg (n = 5).[52] Similarly, biapenem mean area under the plasma concentration-time curve (AUC) values increased with dose in an almost linear manner. After single doses of 150, 300 or 600mg, AUC values were 14.65, 29.24 and 55.35 mg • h/L, respectively.[52]
- During multiple-dose administration, there was no discernible accumulation of biapenem in the plasma of volunteers who received 300 (11 doses in total) or 600mg (nine doses in total) every 12 hours.[52] Biapenem C_{max} values after the first and eleventh doses of 300mg were 15.6 and 14.7 mg/L; after the first and ninth 600mg doses, C_{max} values were 35.7 and 31.5 mg/L, respectively.

Distribution

- Biapenem is widely distributed in the body and penetrates a broad range of body tissues (e.g. lung,

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cervix, myometrium, endometrium, ovary) and fluids (e.g. sputum, pleural effusion, abdominal cavity fluid, venous blood in the elbow).[56] After a single 300mg dose, biapenem concentrations of 9 to 24 mg/L were achieved in abdominal cavity fluid (characteristics of study participants not described); in pleural effusion, the biapenem concentration ranged from 4.4 to 9.5 mg/L, and concentrations of up to 9.6 mg/L were measured in pelvic cavity fluid. Sampling time ranged from 0.5 to 2 hours after the end of administration.[56] Biapenem showed only minimal serum protein binding (3.7% after a single 300mg dose in six volunteers).[53]

Elimination

- Although some carbapenems (e.g. imipenem) undergo hydrolysis of the β-lactam ring by human renal tubular brushborder DHP-I, biapenem was not hydrolysed to a signficant extent by renal DHP-I in *in vitro* or *in vivo* studies.[7,8,52,58]
- The main route of elimination of biapenem was via renal glomerular filtration in volunteers who received therapeutic dosages of the drug[52] and studies in human volunteers have shown negligible excretion of biapenem in the faeces (reviewed by Nakashima[52]). In volunteers, 63.4% of a single 300mg dose and 64.0% of a single 600mg dose of biapenem were recovered as unchanged drug from the urine within 12 hours of administration.[52]
- There was no evidence of accumulation of biapenem in the urine in volunteers who received multiple doses of the drug.[52] After the first and eleventh doses of 300mg, mean cumulative recovery amounts of biapenem were 63 and 55.5%, respectively; after the first and ninth doses of 600mg, corresponding amounts were 62.8 and 53.8%, respectively.
- In volunteers who received biapenem as single doses of 300 (n = 5) or 600mg (n = 5), mean plasma elimination half-life ($t_{½}$) values were 1.03 and 1.04 hours; corresponding mean total clearance (CL_{tot}) values were 10.45 and 10.94 L/h, and renal clearance values of 6.63 and 7.00 L/h were reported.[52] After multiple doses of 300 or 600mg, $t_{½}$ values were 0.96 and 0.85 hours.
- Evidence of extrarenal elimination of biapenem has also been noted in one investigation.[57] About 46% of a single 500mg dose (given intravenously over 30 minutes) was eliminated via an extrarenal route in eight volunteers.[57]

Special Populations

- Age-related changes in the pharmacokinetic profile of biapenem, administered as single 300 and 600mg intravenous doses 1 week apart, have been documented in healthy elderly volunteers (aged 65 to ≥75 years; n = 10). [55] In five elderly volunteers aged ≥75 years (mean age 77.8 years), mean AUCs of biapenem after each of the two doses of the drug were statistically significantly higher (44.6 and 91.9 mg • h/L; $p < 0.05$) than AUCs in the comparator group of five healthy young male volunteers (mean age 23 years) [26.6 and 66.1 mg • h/L]. Statistically significant ($p < 0.05$) age-related changes in both the CL_{tot}) and renal clearance of biapenem were also reported.
- Age-related alterations in the pharmacokinetic properties of biapenem were attributed to a combination of decreased renal function and decreased lean body mass in the elderly volunteers who participated in this investigation.[55] Importantly, the age-related changes in individual pharmacokinetic parameters were not of a sufficient magnitude to warrant dosage modification in elderly individuals with renal function normal for their age.
- The elimination of biapenem is prolonged in patients with mild to severe renal impairment.[57] After a single 500mg dose of biapenem, median plasma $t_{½}$ values were 1.75, 2.89, and 5.61 hours in patients with mild [glomerular filtration rate (GFR) >2.4 L/h/1.73m^2], moderate (GFR ≥0.9 to ≤2.4 L/h/1.73m^2) and severe renal impairment (GFR <0.9 L/h/1.73m^2), respectively, compared with 1.64 hours in volunteers with normal renal function. CL_{tot} decreased with declining renal function: median CL_{tot} values were 8.94, 4.14 and 2.28 L/h/1.73m^2 in patients with mild, moderate and severe renal impairment, respectively, compared with a median CL_{tot} of 9.06 L/h/1.73m^2 in the volunteers.

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• Substantial amounts of biapenem are removed from the blood by haemodialysis.[54,57] About 90% of biapenem was removed from the blood by haemodialysis in five Japanese patients (aged 39 to 62 years) with end-stage renal disease. Haemodialysis appeared to influence the elimination profile of the drug: during haemodialysis, biapenem had two $t_{1/2}$ phases of 1.16 and 3.33 hours. In contrast, when administered to the same patients on a nonhaemodialysis day, biapenem was eliminated monoexponentially and had a $t_{1/2}$ of 4.4 hours.[54]

3. Therapeutic Trials

The therapeutic efficacy of intravenous biapenem (administered as an infusion over 30 or 60 minutes) has been investigated in adults with complicated intra-abdominal infections (as an adjunct to surgery),[59] lower respiratory infections,[60-62] including bacterial pneumonia, [61,63] and complicated urinary tract infections[64-66] in comparative clinical trials, most of which enrolled >100 patients. In all of these trials, biapenem was compared with intravenous imipenem/cilastatin. Biapenem has also shown efficacy in the treatment of patients with orthopaedic, gynaecological or otorhinolaryngological infections in noncomparative trials;[67,68] these trials are not further discussed in this section.

The trial in patients with intra-abdominal infections,[59] which was conducted in Sweden, was randomised, multicentre and nonblind, and compared biapenem 500mg administered once every 8 hours with imipenem/cilastatin 500/500mg administered once every 6 hours. All other trials reviewed here were conducted in Japan and usually compared biapenem 300mg twice daily with imipenem/cilastatin 500/500mg twice daily,[60-66] although a lower dosage of biapenem (150mg twice daily) was also studied in two dose-comparison trials.[60,66] The Japanese trials were randomised, multicentre and nonblind[60-63] or double-blind[64,65] in design.

All trials reported per-protocol (efficacy evaluable) results; in addition, intention-to-treat data were documented in some trials.[59,61]

Intra-Abdominal Infections

• Biapenem showed clinical and bacteriological efficacy similar to that of imipenem/cilastatin in patients with complicated intra-abdominal infections.[59] 118 patients with complicated intra-abdominal infections received biapenem 500mg every 8 hours (n = 58) or imipenem/cilastatin 500/500mg every 6 hours (n = 60) for up to 13 days. At enrolment, 68.6% of the study population had perforated appendicitis with peritonitis; other diagnoses included perforated small intestine, colonic perforation, perforated peptic ulcer and complicated cholecystitis.

• Using the APACHE II scoring system (score of 0 to 10 = low risk; score of 11 to 20 = moderate risk), patients were grouped according to the severity of illness at baseline. Patients with an APACHE II score >20 were excluded from the efficacy evaluations. Forty three patients in the biapenem group and 40 patients in the imipenem/cilastatin group were both clinically and bacteriologically evaluable.

• Criteria for clinical evaluability were: clinically proven intra-abdominal infection, treatment with either study drug for ≥5 days, continuous monitoring during treatment, and observation at two follow-up assessments 1 to 2 weeks and 4 to 6 weeks after the end of treatment. To be eligible for bacteriological efficacy evaluations, patients were required to be clinically evaluable. An additional requirement was the isolation of ≥1 pathogen sensitive to the study drugs from the infection site before the start of treatment. Categories for bacteriological evaluability were: (i) documented or presumed eradication of the pathogen; (ii) presumed or documented persistence of the pathogen; (iii) indeterminate (i.e. unavailability of culture results for a pathogen in patients with an indeterminated outcome).[59]

• A favourable clinical outcome (clinical cure) was achieved in 65.1% (28 of 43) of patients treated

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with biapenem (mean duration of treatment 6.8 days) and in 67.5% (27 of 40) of imipenem/cilastatin recipients (mean duration of treatment 6.4 days). Unfavourable clinical outcomes (clinical failure or indeterminate response) occurred in 34.9% (15 of 43) and 32.5% (13 of 40) of biapenem and imipenem/cilastatin recipients, respectively.[59] Intention-to-treat analysis of clinical outcomes showed that similar proportions of patients in the biapenem (62.1% [36 of 58]) and imipenem/cilastatin groups (61.7% [37 of 60]) achieved a 'satisfactory' response.

• Satisfactory bacteriological responses were reported in 65.1% of biapenem and 67.5% of imipenem/cilastatin recipients. The most common causative aerobic and anaerobic bacteria were *E. coli* and *B. fragilis*.[59]

Lower Respiratory Tract Infections

In the Japanese trials of biapenem in the treatment of patients with lower respiratory tract infections, 'clinical efficacy rates' referred to percentages of patients with 'good' or 'excellent' clinical responses.[60-63] Bacterial eradication rates referred to percentages of patients with presumed or documented eradication of causative pathogens.

• Biapenem showed clinical and bacteriological efficacy similar to that of imipenem/cilastatin (each given for up to 14 days) in adult patients with various types of bacteriologically documented lower respiratory tract infections, such as acute exacerbations of chronic bronchitis, infected bronchiectasis, and bacterial pneumonia.[60-63]

• The efficacy of biapenem 150mg twice daily (low dose) was similar to that of biapenem 300mg twice daily (high dose) or imipenem/cilastatin 500/500mg twice daily (each given for up to 14 days) in a small, randomised, dose-comparison trial in patients with acute exacerbations of chronic bronchitis.[60] *S. pneumoniae*, *S. pyogenes*, *M. catarrhalis*, and *H. influenzae* were among the causative pathogens identified at baseline.

• At the end of treatment, clinical efficacy rates in the biapenem low-dose, biapenem high-dose and imipenem/cilastatin groups were 100% (10 of 10 patients), 90% (9 of 10) and 91.7% (11 of 12, respectively). The high-dose biapenem regimen appeared to have an earlier onset of efficacy than both the low-dose regimen and imipenem/cilastatin, although statistical significance was not reported. On the third day of treatment, clinical efficacy rates in the biapenem low-dose, biapenem high-dose and imipenem/cilastatin groups were 60% (6 of 10), 90% (9 of 10), and 58.3% (7 of 12). A bacterial eradication rate of 100% at the end of treatment was reported for each treatment group.[60]

• Biapenem and imipenem/cilastin were equally effective in the treatment of adults with various chronic respiratory tract infections in a larger trial.[62] Most patients presented with chronic bronchitis, infected bronchiectasis or pulmonary emphysema with infection.[62] At baseline, the most common causative pathogens were *S. pneumoniae*, *H. influenzae* and *P. aeruginosa*. Of the 203 patients allocated to receive either biapenem 300mg twice daily or imipenem/cilastatin 500/500mg twice daily for 14 days, 185 were clinically evaluable. At the end of treatment, clinical efficacy rates in the biapenem and imipenem/cilastatin groups were 90.3% (84 of 93 patients) and 83.7% (77 of 92); bacteriological eradication was achieved in 70.9% (39 of 55 patients) and 66.7% (34 of 51) of biapenem and imipenem/cilastatin recipients, respectively.[62]

• Biapenem 300mg twice daily also demonstrated good efficacy, from day 3 onwards, in the treatment of patients with various lower respiratory tract infections.[61] The efficacy of biapenem was similar to that of imipenem/cilastatin 500/500mg twice daily. Almost half the patients enrolled in this trial (101 of 214) had bacterial pneumonia; lung abcesses, chronic bronchitis, bronchiectasis with infection and pulmonary emphysema with infection were among the other presenting infections, each documented in fewer than ten patients in each treatment group at baseline. The most common causative pathogens were *S. pneumoniae* and *H. influenzae*; five patients in the biapenem group

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and three in the imipenem/cilastatin group had infections caused by *P. aeruginosa*.

• After 14 days' treatment, clinical efficacy rates for evaluable patients were 93.2% (82 of 88 patients) and 91.4% (85 of 93) for the biapenem and imipenem/cilastatin groups, respectively; in the intention-to-treat analysis, clinical efficacy rates were 84.5 and 82%, respectively.[61] As in the dose-comparison trial,[60] biapenem was effective from day 3 onwards; at this timepoint, the clinical efficacy rate was 84.1% (74 of 88) in the biapenem and 76.3% (71 of 93) in the imipenem/cilastatin recipients; the between group difference was not statistically significant. Bacteriological eradication rates were 89.1% (41 of 46 patients) and 97.5% (39 of 40).

• Similarly, biapenem 300mg twice daily produced high clinical and bacteriological response rates (similar to those achieved with imipenem/cilastatin 500/500mg twice daily) in patients with bacterial pneumonia, most of whom had either mild or moderately severe disease. The most common causative pathogens were *S. pneumoniae* and *H. influenzae*. Clinical efficacy rates in the biapenem and imipenem/cilastatin groups were 94.8% (73 of 77 patients) and 92.8% (64 of 69), respectively; bacterial eradication was achieved in 90.9% (20 of 22) of biapenem and 93.1% (27 of 29) of imipenem/cilastatin recipients.[63]

Complicated Urinary Tract Infections

Biapenem has been evaluated in the treatment of patients with complicated urinary tract infections in a small dose-finding trial[66] and in two larger comparative trials.[64,65] In all three trials, the efficacy of 5 days' treatment with biapenem was compared with that of imipenem/cilastatin 500/500mg twice daily for 5 days. Overall clinical efficacy was evaluated as 'excellent', 'moderate' or 'poor' according to criteria proposed by the Japanese Urinary Tract Infection Committee, and was based on numbers of evaluable patients.[64,65] Bacterial eradication rates were defined as the percentage of bacterial strains eradicated or presumed eradicated. Criteria for inclusion in these trials were: pyuria or ≥5 white blood cells per high power field, bacteriuria of $\geq 10^4$ cfu/ml urine, and identifiable underlying urinary tract disease. *E. coli*, *P. aeruginosa* and *E. faecalis*, were the among the most common causative pathogens.[64-66]

• In the dose-finding trial, the optimal dosage of biapenem was 300mg twice daily. Excellent or moderate clinical responses were obtained in 80% (8 of 10 patients), 100% (11 of 11) and 100% (14 of 14) of patients in the biapenem 150mg twice daily, biapenem 300mg twice daily and imipenem/cilastatin groups, respectively.[66] Corresponding bacterial eradication rates for the three groups were 85.7% (12 of 14 strains), 100% (21 of 21) and 94.1% (16 of 17, respectively).

• After 5 days' treatment with biapenem 300mg twice daily, excellent or moderate clinical responses were achieved in 82.7% (81 of 98)[64] and 94.7% (71 of 75)[65] of patients in the two double-blind trials. These response rates did not differ significantly from those obtained with imipenem/cilastatin (77.5 [79 of 102][64] and 93.4% [71 of 76][65]). Similarly, bacterial eradication rates in the biapenem-treated patients (90.2% [147 of 163][64] and 95% [115 of 121][65]) did not differ significantly from those obtained with imipenem/cilastatin (86.3% [139 of 161][64] and 94.4% [117 of 124][65]).

4. Tolerability

• Intravenous biapenem (300 or 500mg twice daily) was generally well tolerated by patients with intra-abdominal infections, lower respiratory tract infections or complicated urinary tract infections.[56,59,61-66,68] In comparative clinical trials,[61-65] adverse events were reported in 1.9 to 3.4% of patients who received biapenem 300mg twice daily, compared with 1.8 to 6.3% of recipients of imipenem/cilastatin 500/500mg twice daily.

• The most common adverse events in comparative clinical trials were skin eruptions/rashes, nausea, vomiting and diarrhoea.[62-65] Similarly, an analysis of tolerability data from 2,323 patients

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treated with biapenem showed that skin rash (incidence 1.0%) and diarrhoea (0.5%) were the most commonly reported adverse events. In total, 57 adverse events were reported in this analysis (overall incidence 2.45%).[56]

• Abnormal clinical test results were reported in 9.5 to 29.5% of patients receiving biapenem 300mg twice daily in clinical trials.[61-65] In addition, pooled data from 2,262 patients showed that 13.1% had abnormal clinical test results.[56] Increased ALT levels (incidence 6.2%), increased AST levels (4.0%), eosinophilia, (3.7%) and decreased creatinine clearance (2.9%) [56,62,65] were the most commonly reported clinical test abnormalities in the pooled data analysis.[56]

5. Dosage and Administration

• In Japan, the recommended dosage of intravenous biapenem is 300mg, administered as an infusion over 30 to 60 minutes, twice daily.[56] Biapenem is available as single 300mg vials and must be reconstituted in 100ml of 0.9% sodium chloride before administration.[56]

6. Current Status

Biapenem is a new parenteral carbapenem antibacterial agent approved for use in Japan. The drug has a broad range of antibacterial activity encompassing many Gram-negative and Gram-positive aerobic and anaerobic bacteria, including species producing β-lactamases. Biapenem is stable to hydrolysis by human renal DHP-I and therefore does not require the coadminstration of a DHP-I inhibitor. Biapenem has shown efficacy, and was generally well tolerated, in the treatment of adults with complicated intra-abdominal infections, lower respiratory tract infections and complicated urinary tract infections.

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