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－Review Article－

Comparison of Four Carbapenems; Imipenem-Cilastatin, Panipenem-Betamipron, Meropenem, and Biapenem with Review of Clinical Trials in Japan

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The development of carbapenem gives a revolutionary impact to the chemotherapy of infectious diseases. The bacteriological and clinical efficacies of carbapenems, including imipenem/cilastatin, panipenem/betamipron, meropenem and biapenem, were evaluated. All four carbapenems were potent against gram-positive and gram-negative bacteria except *Stenotrophomonas maltophilia.* The antimicrobial activities of meropenem against Enterobacteriaceae were slightly superior to other carbapenems. Imipenem and panipenem were slightly more active against gram-positive bacteria than meropenem and biapenem. Biapenem was the most potent against *Acinetobacter anitratus.* The in vitro activity of imipenem was compared between 1990 and 1992 in Nagasaki University Hospital. The resistance rate of *S. aureus,* whose MIC is higher than 25 mg/l, increased from 3% to 22%, *S. pneumoniae,* whose MIC is higher than 0.05 mg/l, increased from 9% to 30% and *P. aeruginosa,* whose MIC is higher than 5 mg/l, increased from 20% to 32%. The isolation rates of *S. maltophilia* from sputum increased gradually from 0.9% in 1984 to 3.5% in 1991.

The clinical efficacy rates of imipenem/cilastatin and panipenem/betamipron were 79% and 77%, and the rates of meropenem and biapenem 100% and 96.2% for the treatment of respiratory infection in our department, respectively. The efficacy rates of imipenem/cilastatin decreased from 79% to 67.7% after being commercialized. This decline was due to administration to patients with severe underlying diseases and with infection caused by resistant strains such as *P. aeruginosa* and *S. aureus.*

The phase II and III trials of carbapenems in internal medicine, which were performed separately in Japan, showed that the clinical efficacy rates were 73%, 79%, 86% and 89%, and the rates of adverse reaction were 4.7%, 3.3%, 1.8% and 2.2% in imipenem/cilastatin, panipenem/betamipron, meropenem and biapenem, respectively. Newly developed carbapenems such as biapenem improved the clinical efficacy although the difference of clinical efficacies between imipenem/cilastatin and other carbapenems was not statistically significant in double-blind comparative studies.

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Introduction

Carbapenem compounds are bactericidal and potent antimicrobial agents with broad spectra against gram-positive and gram-negative bacteria, and more stable against beta-lactamase than cephems. Imipenem/cilastatin has been on commercial preparation in Japan since 1987, followed by panipenem/betamipron in 1993. Meropenem and biapenem have been developed with a great expectancy to be more potent without dehydropeptidase inhibitor than other carbapenems.

The development of carbapenem gives a revolutionary impact to the chemotherapy of infectious diseases, especially severe infection. However, physicians have noticed increase in refractory infection even with carbapenem treatment. We have studied the in vitro activities of 4 carbapenems and evaluated their clinical effects by reviewing phase II and III trials of carbapenems in Japan, including our own experience.

1. Materials and Methods

1.1 In vitro activity of 4 carbapenems against clinical isolates

In vitro susceptibility test was conducted on 27-33 strains of 15 species (270 organisms) isolated from patients in Nagasaki University Hospital in 1993. The micro-broth 2-fold dilution method using the MIC 2000 system (Dynatech Co.) was used to determine the minimum inhibitory concentration (MIC) of each drug. Imipenem, panipenem, meropenem, and biapenem were kindly offered from Banyu, Sankyo, Sumitomo, and

Lederle Japan, respectively.

1.2 The change of susceptibility of clinical isolates to imipenem

The susceptibility of 12 species of clinical isolates in Nagasaki University Hospital to Imipenem was compared between 2640 isolates in 1990 and 3037 isolates in 1992 using the microbroth dilution method mentioned above.

The isolation rates of *S. maltophilia* from sputum were observed in patients in Nagasaki University Hospital from 1984 to 1991.

1.3 The clinical evaluation of 4 carbapenems reviewing from phase II and III trials performed in Japan

The phase II and III trials of imipenem/cilastatin, panipenem/betamipron, meropenem and biapenem were performed independently in Japan (Table 3)./ Imipenem /cilastatin was administered to 529 patients including 419 respiratory infection, 46 urinary tract infection, 35 sepsis, 11 abdominal infection and 18 other infection from 1980 to 1982. Panipenem/betamipron was administered to 446 patients including 396 respiratory infection, 23 urinary tract infection, 19 seps is, 2 abdominal infection and 6 other infection from 1988 to 1990. Meropenem was administered to 567 patients including 532 respiratory infection, 17 urinary tract infection, 6 sepsis, 6 abdominal infection and 6 other infection from 1989 to 1991. Biapenem was administered to 511 patients including 485 respiratory infection, 11 urinary tract infection, 9 sepsis, 5 abdominal infection and 1 other infection from 1991 to 1993. We reviewed their clinical records and individual data were analyzed with kind permission of each pharmaceutical companies.

2. Results

2.1. In vitro activity of 4 carbapenems against clinical isolates

All four carbapenems were potent against gram-positive and gram-negative bacteria except *Stenotrophomonas maltophilia* (*Table 1*). *Their antimicrobial activities were similar against most organisms, however, the antimicrobial activities of meropenem against Escherichia* coli, *Klebsiella pneumoniae, Proteus vulgaris, Citrobacter freundii, Enterobacter cloacae, Pseudomonas aeruginosa,* and *Hemophilus influenzae* were superior to those of imipenem, panipenem and biapenem. Imipenem and panipenem were slightly more active against methicillin sensitive-*Staphylococcus aureus* (MSSA), *S. epidermidis* and *E. faecalis* than meropenem and biapenem. Panipenem was the most potent against penicillin resistant *Streptococcus pneumoniae.* Biapenem was the most potent against *A. anitratus.* However, antimicrobial activities of 4 carbapenems were generally similar in most bacteria.

Table 1. In vitro antibacterial activities of 4 carbapenems

Organisms (no. of strains)	Drugs	MIC(mg/L) range	MIC50	MIC90
Methicillin sensitive-Staphylococcus aureus (27)	Imipenem	<0.03	<0.03	<0.03
	Panipenem	<0.03	<0.03	<0.03
	Meropenem	0.06-0.12	0.06	0.12
	Biapenem	<0.03-0.12	0.06	0.06
Methicillin resistant-Staphylococcus aureus (32)	Imipenem	<0.03-64	0.12	32
	Panipenem	<0.03-64	0.25	32
	Meropenem	0.12-64	2	32
	Biapenem	<0.03-64	1	32
Staphylococcus epidermidis (33)	Imipenem	<0.03-32	2.0	4.0
	Panipenem	<0.03-32	0.5	4.0
	Meropenem	0.06-32	2.0	8.0
	Biapenem	<0.03-32	1.0	8.0
Streptococcus pneumoniae (32)	Imipenem	<0.03-0.12	<0.03	<0.03
	Panipenem	<0.03	<0.03	<0.03
	Meropenem	<0.03-0.25	<0.03	<0.03
	Biapenem	<0.03-0.12	<0.03	<0.03

Penicillin G resistant	Imipenem	<0.03-0.25	0.12	0.25
Streptococcus pneumoniae (29)	Panipenem	<0.03-0.12	0.06	0.06
	Meropenem	<0.03-0.5	0.25	0.50
	Biapenem	<0.03-0.25	0.12	0.25
Streptococcus pyogenes (32)	Imipenem	<0.03	<0.03	<0.03
	Panipenem	<0.03	<0.03	<0.03
	Meropenem	<0.03	<0.03	<0.03
	Biapenem	<0.03	<0.03	<0.03
Enterococcus faecalis (32)	Imipenem	0.5-4.0	1.0	2.0
	Panipenem	0.5-4.0	1.0	2.0
	Meropenem	2.0-16	4.0	8.0
	Biapenem	1.0-16	4.0	8.0
Escherichia coli (32)	Imipenem	0.06-0.12	0.06	0.12
	Panipenem	<0.03-0.12	0.06	0.06
	Meropenem	<0.03-0.06	<0.03	<0.03
	Biapenem	<0.03-0.06	<0.03	0.06
Klebsiella pneumoniae (32)	Imipenem	0.06-0.25	0.12	0.25
	Panipenem	0.06-0.5	0.12	0.12
	Meropenem	<0.03	<0.03	<0.03
	Biapenem	<0.03-0.25	0.06	0.25
Proteus vulgaris (28)	Imipenem	0.25-8.0	1.0	4.0
	Panipenem	0.25-4.0	1.0	4.0
	Meropenem	<0.03-0.5	0.06	0.25
	Biapenem	0.06-8.0	0.25	4.0
Citrobacter freundii (28)	Imipenem	0.12-1.0	0.25	1.0
	Panipenem	0.06-2.0	0.12	0.5
	Meropenem	<0.03-1.0	<0.03	0.12
	Biapenem	<0.03-0.25	0.06	0.25
Enterobacter cloacae (29)	Imipenem	0.12-1.0	0.25	0.25
	Panipenem	0.06-0.25	0.12	0.25
	Meropenem	<0.03-1.0	<0.03	0.06
	Biapenem	<0.03-0.25	0.06	0.06
Pseudomonas aeruginosa (31)	Imipenem	0.5-64	1.0	8.0
	Panipenem	1.0-64	8.0	16
	Meropenem	0.25-64	0.5	4.0
	Biapenem	0.25-64	0.5	16
Stenotrophomonas maltophilia	Imipenem	4.0-64	>64	>64
(30)	Panipenem	8.0-64	>64	>64
	Meropenem	1.0-64	64	>64
	Biapenem	4.0-64	>64	>64
Acinetobacter anitratus (30)	Imipenem	0.12-0.25	0.12	0.25
	Panipenem	0.06-0.25	0.12	0.25
	Meropenem	0.12-1.0	0.25	1.0
	Biapenem	0.06-0.25	0.12	0.12
Hemophilus influenzae (31)	Imipenem	0.06-2.0	0.5	1.0
	Panipenem	0.06-2.0	0.25	0.5
	Meropenem	<0.03-0.25	<0.03	0.06
	Biapenem	<0.03-4.0	0.5	2.0

2.2. The change of susceptibility of clinical isolates to imipenem

The in vitro activity of imipenem was compared between 1990 and 1992 in Nagasaki University Hospital. MIC90s of *S. aureus, S. pneumoniae* and *P. aeruginosa* increased as shown in Table 2. The resistance rate of *S. aureus,* whose MIC is higher than 25 mg/l, increased from 3% to 22%, because the ratio of methicillin resistant *S. aureus* (MRSA) to all *S. aureus* increased from 27.8% (133/478) in 1990 to 65.5% (491/750) in 1992. *S. pneumoniae,* whose MIC is higher than 0.05 mg/l, increased from 9% to 30% due to the increase of penicillin resistant *S. pneumoniae.* From 14.4% (16/111) in 1990 to 36.5% (42/115) in 1992. *P. aeruginosa,* whose MIC is higher than 5 mg/l, increased from 20% to 32%. However, the susceptibilities of other bacteria such as *H. influenzae, K. pneumoniae,* and *M. catarrhalis* to imipenem did not change.

The isolation rates of *S. maltophilia* from sputum increased gradually from 0.9% in 1984 to 3.5% in 1991.

2.3. The clinical evaluation of 4 carbapenems in Japan

a. Clinical review in Nagasaki University

The clinical studies performed in our department were analyzed including phase II and III trials of 4 carbapenems and phase IV trials of imipenem/cilastatin. The clinical efficacy rates of imipenem/cilastatin (25 patients with respiratory tract infection) and panipenem/betamipron (29 patients with respiratory tract infection) were 79% and 77%, and the rates of meropenem (16 patients with respiratory tract infection) and biapenem (30 patients with respiratory tract infection) were 100% and 96.2%.

The comparison between phase II and III (pre-commercialized), and phase IV trials (post-commercialized) of imipenem/cilastatin showed the decreased rates from 79% (25 patients) to 67.7% (77 patients). This decline of efficacy of imipenem/cilastatin after being commercialized was analyzed by investigating the underlying diseases and isolated organisms in failure

Table 2. The change of susceptibility to imipenem between 1990 and 1992

Organisms	(no. of strains)	Year	MIC(mg/L)		
			range	MIC50	MIC90
Staphylococcus aureus	(478)	1990	<0.05->25	<0.05	5.0
		1992	<0.05->25	2.5	>25
Streptococcus pneumoniae	(111)	1990	<0.05-0.5	<0.05	<0.05
		1992	<0.05-0.5	<0.05	0.5
Enterococcus faecalis	(324)	1990	<0.05-25	1.0	2.5
		1992	<0.05-5.0	1.0	2.5
Moraxella catarrhalis	(36)	1990	<0.05-0.5	<0.05	0.5
		1992	<0.05-0.5	<0.05	0.5
Hemophilus influenzae	(180)	1990	<0.05-25	0.5	2.5
		1992	<0.05-5.0	0.5	1.0
Escherichia coli	(241)	1990	<0.1-1.0	<0.1	<0.1
		1992	<0.1-5.0	<0.1	<0.1
Klebsiella pneumoniae	(149)	1990	<0.1-5.0	<0.1	1.0
		1992	<0.1-5.0	<0.1	1.0
Citrobacter freundii	(34)	1990	<0.1-5.0	1.0	1.0
		1992	<0.1-5.0	1.0	1.0
Enterobacter cloacae	(189)	1990	<0.1-10	1.0	1.0
		1992	<0.1-25	1.0	1.0
Pseudomonas aeruginosa	(695)	1990	<0.1->100	1.0	10
		1992	<0.1->100	1.0	25
Stenotnophomonas maltophilia	(84)	1990	1.0->100	>100	>100
		1992	1.0->100	>100	>100
Acinetobacter anitratus	(119)	1990	<0.1-5.0	0.1	1.0
		1992	<0.1-5.0	0.1	1.0

cases treated by imipenem. *P. aeruginosa* and *S. aureus* were isolated from 7 and 5 of 22 non-responder failure patients in phase IV, respectively, comparing to 2 *P. aeruginosa* of 5 failure patients in phase II and III trials. The incidence of malignacies in failure cases increased from 4% (1/25) to 23% (18/77) after being commercialized. According to these data, imipenem was used for the treatment of infection of resistant organisms or in immunocompromised patients.

b. Clinical review in Japan

The phase II and III trials of carbapenems in internal medicine, which were performed separately in Japan, were reviewed to evaluate their efficacy and adverse reaction. The clinical efficacy rates increased from 73% of imipenem/cilastatin to 89.2% of biapenem and adverse reaction rates decreased from 4.7% of imipenem/cilastatin to 1.8% of meropenem as drugs developed (Table 3).

The clinical efficacies of 4 carbapenems were analyzed in the phase II and III trials with respect to the presence of underlying diseases and complication. As expected, the efficacy rates were lower in patients with underlying diseases and complication than those without them. Factors of failure in patients treated with carbapenems in the phase II and III trials were analyzed Table 4. Isolated organisms such as *P. aeruginosa* and *S. aureus* could be the main cause for failure of the therapy. *P. aeruginosa* was isolated at the rate of 64% (50/78) in failure patients treated with imipenem/cilastatin, 67% (28/42) in panipenem/betamipron, 69% (22/32) in meropenem, and 60% (9/15) in biapenem. *S. aureus* was isolated at the rate of 8% (6/78) in failure patients treated with imipenem/cilastatin, 10% (4/42) in panipenem/betamipron, 19% (6/32) in meropenem and 13 % (2/15) in biapenem.

The clinical efficacies of 4 carbapenems in respiratory infection were investigated. The overall efficacy rates were 72% in imipenem, 78% in panipenem, 86% in meropenem, and 90% in biapenem. The efficacy rates in chronic bronchitis, bronchiectasis, pulmonary emphysema, and respiratory infection with old pulmonary tuberculosis or diabetes mellitus were similar to overall efficacy of respiratory infection, however, the efficacy rates in diffuse panbronchiolitis and lung cancer were lower than other respiratory infection.

The clinical efficacies in respiratory infection with respect to the isolated organisms were analyzed. However, the clinical efficacy against *P. aeruginosa* respiratory infection was improved from 54% in imipenem to 80% in biapenem. This could be the main reason for improvement of efficacy in overall internal medicine department as a whole.

Table 3. Review of 4 carbapenems in phase II & III in Japan

Drug	No of patients	Clinical efficacy rate	Adverse reaction rate
Imipenem/Cilastatin	529	73%	4.7%
Panipenem/betamipron	446	78.9%	3.3%
Meropenem	567	86.2%	1.8%
Biapenem	511	89.2%	2.2%

Table 4. Isolated organisms from failure patients treated with carbapenem

Organism	Imipenem	Panipenem	Meropenem	Biapenem
Pseudomonas aeruginosa	50(64%)	28(64%)	22(69%)	9(60%)
Staphylococcus aureus	6(8%)	4(10%)	6(19%)	2(13%)
Hemophilus influenzae	2(3%)	2(5%)	-	2(13%)
Enterococcus faecalis	3(4%) 1(7%)		-	2(6%)
Enterobacter cloacae	2(3%)	-	-	1(7%)
Others	15(19%)	8(21%)	2(6%)	2(13%)
Total	78	42	32	15

3. Discussion

The carbapenems are characterized by having an unsaturated bond between C2 and C3 and a carbon atom replacing sulphur at position 1 of the thiazolidine ring. Imipenem is combined with cilastatin, an dehydropeptidase inhibitor, and panipenem with betamipron, because imipenem and panipenem are not stable to renal dehydropeptidases and they are nephrotoxic in certain animals (Kropp et al. 1982). Meropenem and biapenem are stable to renal dehydropeptidases (Edwards et al. 1989; Ubukata et al. 1990), and they do not require concomitant administration of an enzyme inhibitor.

Figure 1 shows the structure of carbapenem drugs. Degradation by hydropeptidase of kidneys causing unstability is a disadvantage for imipenem and panipenem. On incubation with human renal dehydroxypeptidase I (DHP-1) for two hours, degradation of imipenem, panipenem and meropenem were 100%, 78% and 48% respectively, but about 10% for biapenem. Toxicity to central nervous system and kidney are also considerable.

Cylastatin sodium, an enzyme inhibitor has been combined at 1:1 ratio with imipenem in order to inhibit

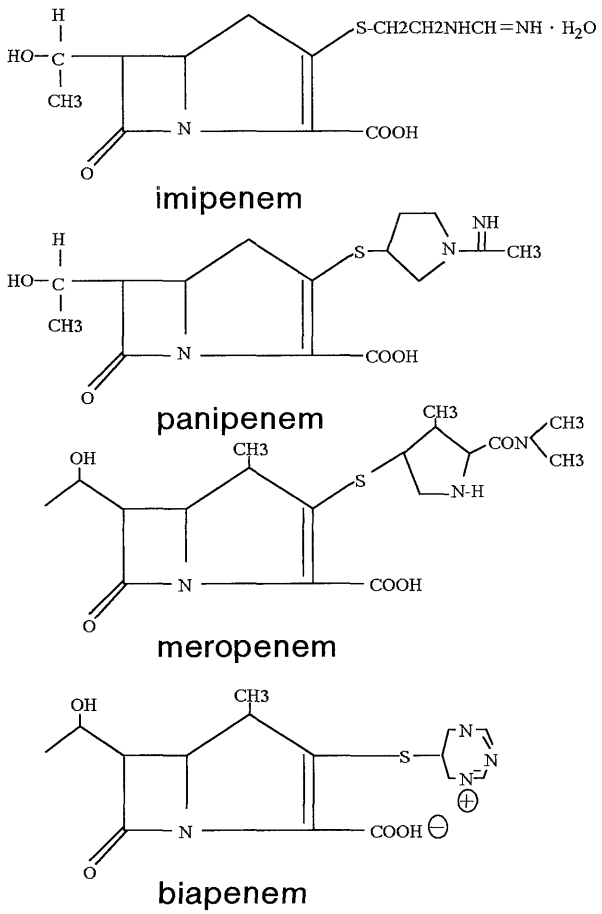

Fig. 1 structure of carbapenems

renal uptake. Panipenem in high dose administration causes nephrotoxicity. So, combination with betamipron at 1:1 ratio is done to lower nephrotoxicity. Betamipron has no antimicrobial activity, but improves safety, and reduction in nephrotoxicity has been documented. Meropenem is stable to enzyme DHP-I, and is less nephrotoxic; thus single drug administration is possible. Biapenem is stable for DHP-I, has no toxic effects on kidney, so like meropenem single drug administration is possible. High toxicity to CNS has been reported clinically with earlier carbapenems. In rabbits, no abnormality in electroencephalogram and movement has been observed with biapenem. The reason was thought to be poor penetration through the blood brain barrier, and very weak affinity for GABA-receptor and glycine-receptor has been suggested.

Thus newer developments of carbapenems resulted in reduction of nephrotoxicity and toxicity to the CNS. In addition, single drug administration has been made possible.

In vitro activity of carbapenems is very potent against both gram-positive and gram-negative pathogens except *S. maltophilia*. The highest MICs were obtained with *S. maltophilia*, an MIC50 of $>$ 64 mg/l being demonstrated for all compounds tested. This may explain the gradual increase of isolation rates from sputum in Nagasaki University Hospital. Some strains of *MRSA*, *S. epidermidis*, *E. faecalis* and *P. aeruginosa* are not sensitive to carbapenems. All carbapenems were very active against the bacteria tested, however, MIC90s were slightly affected by the penicillin-resistant strains. No Enterobacteriaceae were resistant to carbapenems and meropenem was the most potent to most of the tested Enterobacteriaceae. Meropenem is reported to be more active than imipenem against most of the members of the family Enterobacteriaceae, but less active against gram-positive aerobic species (Edwards et al. 1989). This tendency is also true in the relationship between biapenem and imipenem (Yoshida & Mitsuhashi 1990; Neu et al. 1992; Catchpole et al. 1992; Malanoski et al. 1993). Sader & Jones (1993) reported that imipenem, meropenem and biapenem are potent to Enterobacteriaceae, *P. aeruginosa* and *Bacteroides fragilis* but not active against *S. maltophilia*, oxacillin-resistant *Staphylococcus* spp. and *Enterococcus* spp.

The rapid increase of resistant strains of *S. aureus*, *S. pneumoniae* and *P. aeruginosa* to imipenem is a problem in Nagasaki University Hospital. MRSA increased from 27.8% in 1990 to 65.6% in 1992, and penicillin-resistant *S. pneumoniae* from 14.4% in 1990 to 36.5% in 1992. This plays an important role of decreased clinical efficacy of imipenem in Nagasaki University Hospital after being commercialized.

Clinical efficacies of four carbapenems in phase II & III trials in Japan were reanalyzed. Biapenem demonstrated the highest efficacy rate and meropenem showed the lowest rate of adverse reaction among four carbapenems (Shinyaku Symposium 1984; Shinyaku Symposium 1990; Shinyaku Symposium 1991; Shinyaku Symposium 1993). Isolated organisms were also analyzed in failure patients treated with these carbapenems, and *P. aeruginosa* and *S. aureus* were the major isolates.

Double blind comparative studies between imipenem and other 3 carbapenems were performed in Japan. The comparative studies for pneumonia among three groups; between panipenem/betamipron (1g/day) and imipenem/cilastatin (1g/day), meropenem (0.5g/day) and imipenem/cilastatin (1g/day) and biapenem (600mg/day) and imipenem/cilastatin (1000mg/day), as phase III trials performed in Japan, revealed no significant difference between imipenem and other carbapenems, however, only biapenem showed better clinical efficacy rate (94.8%) than imipenem/cilastatin (92.8%) (Hara et al. 1992; Hara et al. 1992; Matsumoto et al. 1995).

Most carbapenems have been developed in Japan, and they are regarded to be an all-mighty antibiotic due to their potent antimicrobial activity and wide spectrum. However, the present study suggested that administration of carbapenems to patients with severe underlying disease or infection caused by less sensitive organisms such as *P. aeruginosa* and MRSA may reduce its value for one of the best antibiotics.

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