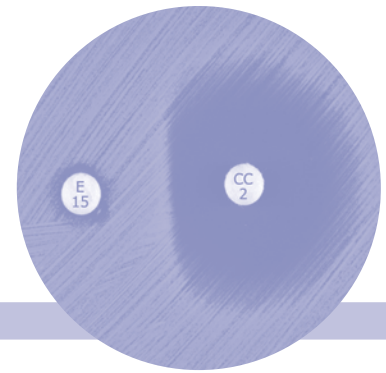


# the d-zone

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## Study of the Month

In the first randomized, prospective, double-blind, placebo-controlled trial of vancomycin vs. metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, vancomycin appears superior for severe disease.

Zar FA, Bakkanagari SR, Moorthi KM, et al.

A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 45 (3): 302-7, 2007.

## Review of the Month

Wagenlehner and colleagues emphasize the importance of considering pharmacokinetic and pharmacodynamic principles when choosing antibiotics for urosepsis.

Wagenlehner FM, Weidner W, Naber KG.

Pharmacokinetic characteristics of antimicrobials and optimal treatment of urosepsis. Clin Pharmacokinet 46 (4): 291-305, 2007.

## Quote of the Month

"I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel."

-Maya Angelou

## the d-zone

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## Doripenem, the next carbapenem

### Carbapenems: their brief history

Bacterial resistance continues to increase at an alarming rate. The rapid rise to prominence of vancomycin-resistant *Enterococcus* (VRE), penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP), and community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has helped fuel the recent development of new agents for Gram-positive infections, such as daptomycin. However, there is also a need for innovative tools to combat highly resistant Gram-negative pathogens such as *Acinetobacter*, *Enterobacter*, and *Pseudomonas aeruginosa*.

Until the discovery of thienamycin (the first carbapenem) in the mid-1970s,  $\beta$ -lactam development consisted of dozens of chemical modifications to the classical penicillin ("penam") and cephalosporin ("cephem") nuclei. The carbapenem class can be considered a "hybrid" of those two nuclei (see Figure 1). Thienamycin, produced by the soil organism *Streptomyces cattleya*, was immediately recognized for its exceptionally broad spectrum of activity and resistance to destruction by bacterial  $\beta$ -lactamases. Imipenem, the more stable N-formimidoyl derivative of thienamycin, was unfortunately subject to rapid conversion *in vivo* to a nephrotoxic metabolite by mammalian dihydropeptidase I (DHP-1), located in renal proximal tubule cells. However, coadministration of imipenem with the DHP-1 inhibitor cilastatin prevented this conversion and resulted in a safe and effective product for human use.<sup>1</sup>

Imipenem received Food and Drug Administration (FDA) approval in 1985. Meropenem, the next carbapenem, was approved in 1996. Advantages of meropenem include stability to metabolism by DHP-1 (because of the 1- $\beta$  methyl substituent on the carbapenem nucleus), slightly greater potency against Gram-negative pathogens than imipenem (at the expense of decreased Gram-positive activity), and less risk of neurotoxicity.<sup>2</sup> Ertapenem, the third carbapenem (approved by the FDA in 2001), has a half-life of nearly four hours. This allows for once-daily dosing, which is arguably the drug's best feature. The antibacterial spectrum of ertapenem is limited; notable deficiencies include *P. aeruginosa*, *Acinetobacter*, and *Enterococcus*.<sup>3</sup>

Recently, the Clinical Laboratory Standards Institute (CLSI) incorporated the carbapenem class of drugs into a larger grouping known simply as the "penems," consisting of two subclasses, penems and carbapenems (see Figure 2).

Doripenem (S-4661), initially under development in the United States by Peninsula Pharmaceuticals, is now part of Johnson & Johnson's (J&J) Anti-infective Research and Development portfolio following the company's acquisition of Peninsula in 2005. Doripenem is licensed from Shionogi & Co., Ltd., which launched doripenem in Japan in September, 2005. In June of this year, J&J announced the submission of a New Drug Application (NDA) to the US FDA for treatment of nosocomial pneumonia. The nosocomial pneumonia indication has been granted "fast-track" status by the FDA. An NDA for the treatment of complicated intraabdominal infection and complicated urinary tract infection was previously submitted by J&J in December of 2006. Pending regulatory approval, the drug will be marketed in the US by Ortho-McNeil, Inc. Doripenem is the major focus of this month's *D-Zone*.

## Doripenem, the next carbapenem (continued)

### Mechanism of action

Doripenem exerts its bactericidal effect by binding to certain penicillin-binding proteins (PBPs), membrane-associated bacterial enzymes involved in peptidoglycan (cell wall) synthesis. Like other carbapenems, doripenem has the highest binding affinity for PBP 2.<sup>4</sup> Drug binding to PBP 2 produces cell lysis without prior filamentation, in contrast to drugs that bind primarily to PBP 3 (such as third-generation cephalosporins). Preferential binding to PBP 2 thus results in a smaller increase in cell mass, and consequently less endotoxin release, before cell death.<sup>5</sup>

### Antimicrobial activity of doripenem

Pooled MIC<sub>90</sub> carbapenem susceptibility data is summarized in Table 1, adapted from Zhanel et al.<sup>5</sup> Doripenem is similar to imipenem in potency against most common Gram-positive aerobic organisms, including penicillin-nonsusceptible strains of *S. pneumoniae*. No carbapenem demonstrates useful activity against *E. faecium* or MRSA. The activity of doripenem against Gram-negative aerobic organisms is generally equivalent to meropenem; potency against *P. aeruginosa* is slightly superior to the other carbapenems, whereas the activity of doripenem against *Acinetobacter* is comparable. Extended-spectrum  $\beta$ -lactamase (ESBL) production has little impact on the activity of doripenem against *Escherichia coli* and *Klebsiella pneumoniae*. Antianaerobic activity is similar to the other carbapenems.

### Pharmacokinetics and pharmacodynamics

Single-dose carbapenem pharmacokinetic parameters appear in Table 2, adapted from Zhanel et al.<sup>5</sup> All currently marketed carbapenems are for parenteral administration only. The drugs penetrate most body fluids and tissues well. The high protein binding of ertapenem results in a prolonged elimination half-life that allows for once-daily dosing. Doripenem, imipenem, and meropenem are mainly eliminated in the urine as unchanged drug; 80% of ertapenem appears in the urine, half as parent compound and half as the open  $\beta$ -lactam ring degradation product of DHP metabolism. All four drugs require some degree of dosage adjustment in renal insufficiency.

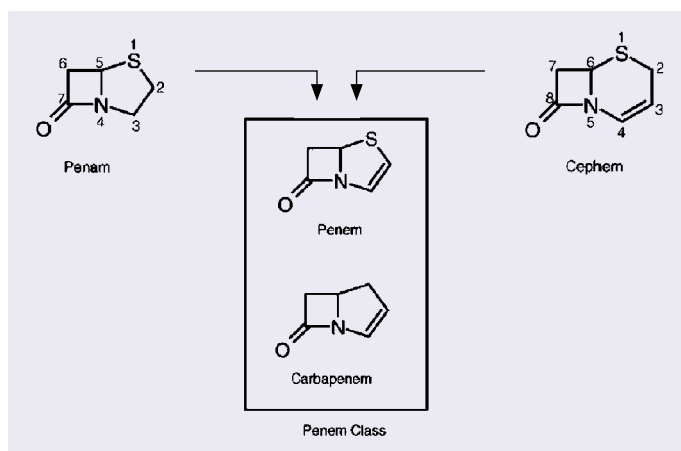


Figure 1. The chemistry of the penams, cepems, and penems<sup>9</sup>

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Ertapenem, imipenem, and meropenem exhibit time-dependent pharmacodynamics; for optimum bactericidal activity, drug concentrations should exceed the MIC for at least 40% of the dosage interval. Unlike other  $\beta$ -lactams, these three carbapenems also exhibit a postantibiotic effect (PAE) against both Gram-positive and Gram-negative bacteria.<sup>5</sup> There are currently no published data describing the pharmacodynamic behavior of doripenem.

### Mechanisms of resistance

Production of  $\beta$ -lactamase is a common bacterial defense mechanism, with over 400 different  $\beta$ -lactamases described so far. However,  $\beta$ -lactamases with the ability to hydrolyze carbapenems (carbapenemases) are relatively rare.  $\beta$ -lactamases are classified into four molecular classes based on amino acid homology (Ambler class A through D) or functionally according to their substrate spectrum and sensitivity to  $\beta$ -lactamase inhibitors (Bush classification scheme). Doripenem, like other carbapenems, is generally stable toward hydrolysis by Ambler class A, C, and D enzymes (serine  $\beta$ -lactamases), including ESBLs and inducible AmpC  $\beta$ -lactamases. However, class A enzymes of Bush group 2f (NMC, IMI, SME, and KPC enzymes) include carbapenems in their substrate profile. These enzymes have appeared sporadically in clinical isolates of *Enterobacter cloacae*, *Serratia marcescens*, and *Klebsiella spp.* since their original discovery in the mid-1980s. The genes encoding the NMC, IMI, and SME enzymes tend to be located on the bacterial chromosome, whereas the KPC enzymes are encoded on transferable plasmids.<sup>6</sup>

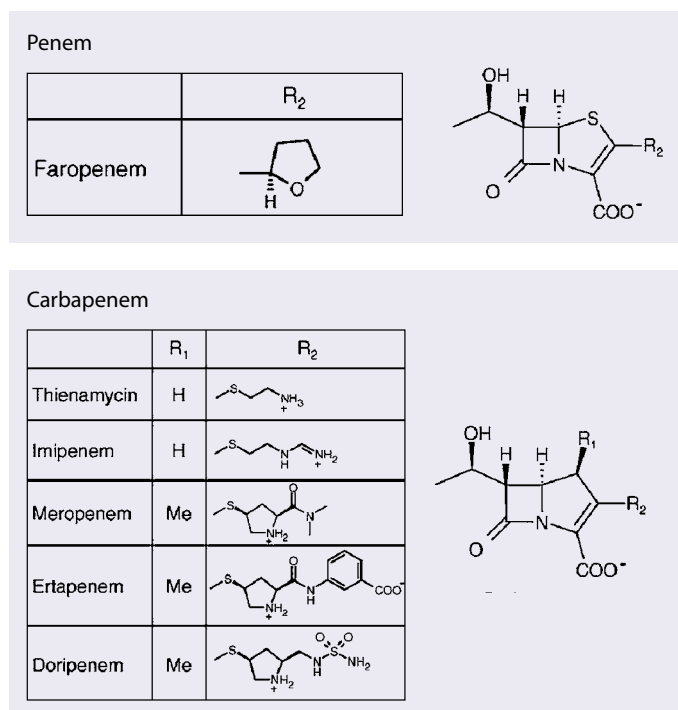


Figure 2. The penems and carbapenems<sup>9</sup>

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## Doripenem, the next carbapenem (continued)

Table 1. *In vitro* carbapenem activity (MIC<sub>90</sub>)<sup>5</sup>

	DORIPENEM	ERTAPENEM	IMIPENEM	MEROPENEM
<b>GRAM-POSITIVE AEROBES</b>				
<i>Enterococcus faecalis</i>	8	16	4	16
<i>Enterococcus faecium</i>	>16	>16	>8	>16
<i>Listeria monocytogenes</i>	NA	0.5	0.12	0.12
<i>Streptococcus agalactiae</i>	0.016	0.06	0.016	0.06
<i>Streptococcus pneumoniae</i> (PSSP)	≤0.008	0.015	≤0.008	≤0.008
<i>Streptococcus pneumoniae</i> (PISP)	0.25	1	0.12	0.5
<i>Streptococcus pneumoniae</i> (PNSP)	1	2	1	1
<i>Streptococcus pyogenes</i>	≤0.008	≤0.008	≤0.008	≤0.008
<i>Staphylococcus aureus</i> (MSSA)	0.06	0.25	≤0.5	0.12
<i>Staphylococcus aureus</i> (MRSA)	16	>32	32	32
<b>GRAM-NEGATIVE AEROBES</b>				
<i>Acinetobacter</i> spp.	1	>8	0.25	1
<i>Citrobacter freundii</i>	0.03	≤0.015	1	0.03
<i>Enterobacter cloacae</i>	0.06	0.06	2	0.06
<i>Escherichia coli</i>	0.03	≤0.06	≤0.5	0.03
<i>Escherichia coli</i> (ESBL-producing)	0.06	0.25	≤0.5	0.06
<i>Haemophilus influenzae</i>	0.5	0.12	4	0.25
<i>Klebsiella oxytoca</i>	0.06	≤0.015	0.5	0.03
<i>Klebsiella pneumoniae</i>	0.06	≤0.06	1	0.03
<i>Klebsiella pneumoniae</i> (ESBL-producing)	0.12	0.5	1	0.12
<i>Moraxella catarrhalis</i>	0.03	0.008	0.12	≤0.008
<i>Morganella morganii</i>	0.5	0.03	4	0.12
<i>Neisseria gonorrhoeae</i>	NA	0.03	0.016	NA
<i>Proteus mirabilis</i>	0.25	≤0.06	2	0.06
<i>Proteus vulgaris</i>	0.5	0.25	4	0.12
<i>Pseudomonas aeruginosa</i>	8	>8	>8	16
<i>Salmonella</i> spp.	0.06	≤0.06	≤0.5	0.03
<i>Serratia marcescens</i>	0.25	0.12	2	0.06
<i>Shigella</i> spp.	0.06	≤0.06	≤0.5	0.03
<i>Stenotrophomonas maltophilia</i>	>16	>8	>8	>16
<b>ANAEROBES</b>				
<i>Bacteroides fragilis</i>	1	0.5	0.5	0.5
<i>Clostridium difficile</i>	2	4	4	4
<i>Clostridium perfringens</i>	NA	0.06	0.12	≤0.06
<i>Fusobacterium</i> spp.	1	1	1	0.12
<i>Peptostreptococcus</i> spp.	NA	0.12	0.06	0.12
<i>Prevotella</i> spp.	0.25	4	0.5	0.25

## GLOSSARY:

NA = information not available

*S. pneumoniae*: PSSP = penicillin-susceptible, PISP = intermediate-susceptible, PNSP = non-susceptible*S. aureus*: MSSA = methicillin-susceptible, MRSA = methicillin-resistant

ESBL = extended-spectrum β-lactamase

Queenan et al. investigated the ability of imipenem, meropenem, and doripenem (along with ceftaxime and ceftazidime) to induce AmpC expression in various Enterobacteriaceae and *P. aeruginosa*. Ceftaxime was the strongest inducer, followed by imipenem. Doripenem and meropenem were similar in their induction profiles and at least two-fold less than imipenem. Ceftazidime, as expected, was weakest.<sup>7</sup>

Doripenem and other carbapenems are naturally susceptible to hydrolysis by Ambler class B enzymes, also known as Bush group 3 enzymes or zinc metallo-β-lactamases. These enzymes possess broad substrate specificity and resistance to commercially available β-lactamase inhibitors. The first metallo-β-lactamases widely studied were chromosomally

encoded enzymes from *Aeromonas* spp., *Bacillus cereus*, and *Stenotrophomonas maltophilia*. Recently, there has been a significant increase in the detection and spread of readily transferable metallo-β-lactamases (VIM, IMP, GIM, and SIM enzymes).

Imipenem resistance in *P. aeruginosa* results from loss of the OprD porin (the aqueous channel in the cell membrane through which the drug gains access to the interior) coupled with activity of AmpC β-lactamase.<sup>5</sup> In fact, porin loss is the most common mechanism associated with imipenem resistance in *P. aeruginosa*. Doripenem (and meropenem) appear to additionally require the expression of drug efflux pumps for resistance to be conferred, which may help explain the superior antipseudomonal activity of these two carbapenems.

## Clinical trials

There are currently no clinical trials of doripenem published in the medical literature. A study comparing doripenem to meropenem for the treatment of complicated intraabdominal infection was summarized at the 46<sup>th</sup> annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting in San Francisco in 2006. Using a prospective, multicenter, double-blind, double-dummy study design, 486 patients diagnosed with complicated intraabdominal infection were randomized to treatment with doripenem (500 mg IV q8h over 60 minutes) or meropenem (1 gm IV q8h over 3–5 minutes). After nine or more doses of intravenous study drug, patients could be switched to oral therapy (amoxicillin/clavulanic acid 875/125 mg PO bid) if specific criteria were met; total study duration was 5–14 days. In the microbiologically evaluable patients (baseline pathogen isolated from an abdominal culture) at the test-of-cure (TOC) visit (28–42 days after the last dose of study drug), the clinical cure rate was 83.3% for doripenem versus 83.0% for meropenem. Microbiologic eradication rates in the treatment arms at the TOC visit were also comparable.<sup>8</sup>

## Adverse effects

Information about adverse effects of doripenem is limited. In the intraabdominal infection trial summarized above, the most common adverse effects in doripenem-treated patients were nausea (9.5%, vs. 9.4% with meropenem), diarrhea (7.4%, vs. 7.7% with meropenem), anemia (7.0%, vs. 3.9% with meropenem), and vomiting (6.6%, vs. 6.9% with meropenem).<sup>8</sup>

β-lactam antibiotics in high doses have been associated with seizures, possibly due to inhibition of gamma-aminobutyric acid (GABA) receptor binding.<sup>9</sup> Carbapenem affinity for the GABA<sub>A</sub> receptor correlates with the relative basicity of the R-2 side chain (see Figure 2): the more basic the side chain, the more neurotoxic the drug. Based on this observation, the relative neuroexcitatory potential of the three antipseudomonal carbapenems would be imipenem > meropenem > doripenem. Although confirmatory human data are lacking, doripenem produced no proconvulsive activity in rats following intravenous or intracerebroventricular administration.<sup>10</sup>

## Doripenem, the next carbapenem (continued)

Table 2. Single-dose carbapenem pharmacokinetics<sup>5</sup>

	Dose (gm)	Cmax (µg/ml)	AUC (mg·h/L)	t <sub>1/2</sub> (h)	Vd (L/kg)	% protein bound	% excreted in urine as unchanged drug
<b>DORIPENEM</b>	0.5	20.2	44.1	0.93	NA	8.9	75
<b>ERTAPENEM*</b>	1	154.9 (22.0)	572.1 (68.6)	3.8	8.2 (1.5)	92–95	44
<b>IMIPENEM</b>	0.5	30–35	42.2	1	0.23–0.31	20	60–70
<b>MEROPENEM</b>	1	50–60	66.9–77.5	1	0.23–0.35	2	70

\*values corresponding to free drug are in parentheses

NA = not available

### Drug interactions

No drug interactions in humans involving doripenem have been reported. Meropenem reduces plasma concentrations of valproic acid, apparently by enhancing glucuronidation; this interaction has also been reported with imipenem and ertapenem.<sup>11</sup> Doripenem has been shown to decrease valproic acid concentrations in animals.<sup>12</sup>

### Other penems

Biapenem and panipenem have been marketed in Asia but are not undergoing development for other markets. Tebipenem, an orally active carbapenem, is currently in phase II study in Japan. Faropenem medoxomil is an orally active penem (see Figure 2). The bioavailability of the original sodium salt was 20–30%, but formulation as an ester boosts oral bioavailability to 70–80%. Other features of faropenem medoxomil include reliable β-lactamase stability (including ESBLs and AmpC β-lactamases), low induction potential, and a marked PAE against *S. pneumoniae* and other organisms. The drug, which lacks antipseudomonal activity, has an attractive antibacterial spectrum for ambulatory patients.<sup>13</sup>

These features suggest a role for faropenem medoxomil as “switch therapy” or “step-down” therapy. However, in late 2006 the FDA issued a non-approvable letter to Replidyne, the company developing faropenem medoxomil for use in the US, recommending further clinical study.

### Conclusion

Doripenem is a new, well-tolerated parenteral carbapenem that combines the Gram-positive activity of imipenem with the Gram-negative activity of meropenem. The drug lacks activity against pathogens that are typically carbapenem-resistant. Whether the improved antipseudomonal potency of doripenem offers clinical benefit is not known. Data concerning cross-resistance between doripenem and the other carbapenems for nonfermenting Gram-negative bacilli such as *Acinetobacter* will be helpful. Pricing information is not yet available.

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