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REVIEW

Pharmacotherapy of Complicated Urinary Tract and Intra-abdominal Infections with Doripenem

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Abstract: Due to the growing rate of multi-drug resistant bacteria in complicated infections, the need for new broad-spectrum antimicrobials is paramount. Doripenem, a new addition to the intravenous carbapenem class, has recently been approved for the treatment of complicated lower urinary tract infections and/or pyelonephritis (cUTI) and complicated intra-abdominal infections (cIAI) in adult patients. Doripenem exhibits potent *in vitro* and *in vivo* bactericidal activity against an assortment of Gram-positive and Gram-negative aerobic and anaerobic organisms, including *Pseudomonas aeruginosa, Acinetobacter baumannii*, and Enterobacteriaceae that produce extended spectrum beta-lactamases (ESBL). Relative to other available carbapenems, doripenem typically displays MICs that are 1–2 dilutions lower than meropenem and 2–4 dilutions lower than imipenem against *P. aeruginosa*. Since the kidneys primarily excrete doripenem as whole drug, dose adjustments are needed in patients with renal impairment. Doripenem 500 mg q8 h demonstrated non-inferiority to levofloxacin 250 mg q24 h in clinical trials of patients with cUTI; it was non-inferior to meropenem 1000 mg q8 h in patients with cIAI. Doripenem's broad spectrum of activity, *in vitro* potency against particularly difficult to treat organisms, and desirable safety profile make it an attractive option in the treatment of cUTI and cIAI.

Keywords: doripenem, complicated urinary tract infections, intra-abdominal infections, carbapenem

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Introduction

In the last decade, a global rise of multi-drug resistant organisms has dramatically reduced the number of available antibiotic treatment options.[1–5] Patients infected with multidrug resistant organisms commonly have poor clinical outcomes, prolonged hospital stays, and greater hospital costs when compared with antibiotic susceptible strains,[6,7] thus posing a serious health care concern in critically ill patients. This scenario is evermore present in difficult to treat infections, such as complicated intra-abdominal (cIAI) and complicated urinary tract infections (cUTI). When such infections are not treated appropriately within a short timeframe (i.e. ≤24 h), they have often led to further complications that may increase morbidity and mortality.

Complicated IAI are best described as infections that initiate at a foci and disseminate to the peritoneal space. Consequently, this leads to peritonitis and abdominal abscesses.[8,9] Moreover, the pathogens responsible for this occurrence of cIAI depend on the location at which it was acquired, such as the community or hospital, and upon the location within the body in which the infection originated. For the most part, Enterobacteriaceae (i.e. *Escherichia coli*, *Proteus* species, *Enterobacter* species), *Enterococcus*, *Streptococcus*, and *Bacteroides* species are regarded as the primary causative pathogens in cIAI.[8] Drug resistant organisms, including *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus*, among others, become more problematic in tertiary peritonitis or infections acquired in the hospital setting. In order to better cover for the organisms causing community or nosocomial acquired cIAI, broad-spectrum antibiotics, either alone or combination, are often regarded as appropriate empiric therapy.[8]

The need for broad-spectrum agents has also been important in treating cUTIs[10–12] because the tendency for patients to be infected with resistant organisms is higher than in uncomplicated urinary tract infection.[10] Patients with cUTIs are those with a structural or functional abnormality of the genitourinary tract.[11,12] The most common pathogen is *E. coli*, but other Gram-negative bacilli pose as potential infectious threats as well. *P. aeruginosa* can be extremely problematic due to the high rates of morbidity and mortality associated with it.[10,13] Additionally, *P. aeruginosa* have a high propensity to develop antibiotic resistance while still maintaining virulence.[1,13]

In spite of this growing epidemiologic and microbiologic problem, the carbapenem class has retained their activity to most bacterial pathogens and their resistance mechanisms.[4,5,14] Recently, a newly developed 1-β-methyl carbapenem, doripenem, received United States Food and Drug Administration (US FDA) approval for the treatment of cUTI and cIAI.[15] This paper will review doripenem characteristics as they pertain to the pharmacology, microbiology, and treatment of cUTI and cIAI.

Pharmacology and Mechanism of Action

Doripenem is a parenteral, broad-spectrum antibiotic with a methyl group at the 1-position that allows for stability when it undergoes renal excretion. Moreover, doripenem also possesses a unique 2-position side chain that provides stability against β-lactamases and added affinity to the binding site.[16–18] As depicted in Figure 1, doripenem has a similar structure to other carbapenems. It has a 4-member lactam ring that is bound to a 5-member thiazolidinic

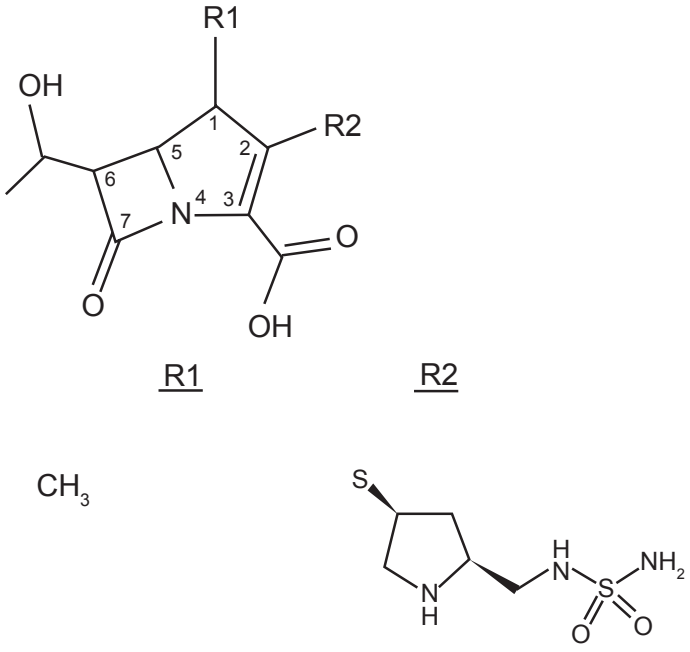

Figure 1. Doripenem chemical structure. **R1**) Methyl-group: Increases stability toward hydrolysis by dehydropeptidase-I (DHP-I). **R2**) Side Chain: Confers high level of *in vitro* activity by increasing protein-binding affinity. Also contributes to the increased drug stability for maintaining ≤12 h at room temperature conditions in normal saline.

ring; however, it is unique with the addition of a sulfamoylaminoethyl-pyrrolidnylthio group side chain on position 2.[16,19] It is thought that this addition increases the acidity of doripenem, which in turn provides for its enhanced *in vitro* activity against *P. aeruginosa*.[16] Moreover, this side chain may also be the reason for the enhanced stability at room temperature, which the other carbapenems (i.e. meropenem and ertapenem) with a similar side chain lack.[20,21] The addition of a β-methyl group at position 1, similar to that found in meropenem and ertapenem, protects doripenem from hydrolysis by dehydropeptidase I (DHP-I) at the renal brush border cells.

Similar to other class members, doripenem achieves bactericidal activity by inhibiting the penicillin binding protein (PBP).[18] The PBP is responsible for maintaining the cell shape of the organism by elongating and cross-linking the peptidoglycan within the bacterial cell wall. When the cell wall is disrupted, it breaks down, which leads to cell lyses and ultimately cell death. Based on the *in vitro* study by Davies and colleagues, doripenem demonstrated a high affinity for the essential PBPs in *E. coli* (PBP-2) and *P. aeruginosa* (PBP-2 and -3). When compared with the other carbapenems, doripenem's PBP affinities were identical to imipenem and meropenem in *E. coli*, but like meropenem, the binding site affinities in *P. aeruginosa* were considerably higher than that of imipenem. The authors suggested that doripenem and meropenem's enhanced PBP affinities in *P. aeruginosa* contributed to the improved anti-pseudomonal activity over that of imipenem.

Microbiology

Analogous to other carbapenems, doripenem possesses *in vitro* activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria but lacks activity against *Stenotrophomonas maltophilia*, *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus*.[22] Aside from these organisms, doripenem has excellent *in vitro* activity against bacteria commonly found in cIAI or cUTI. This is demonstrated by pooled values from various 2008–2009 surveillance studies of MIC 50% and 90% (Table 1).[4,5,14,23,24] Susceptibility breakpoints for the carbapenems vary be drug, organism, and the governing body that defined them [i.e. FDA, Clinical Laboratory Standard Institute (CLSI), and European Union Clinical

Table 1. *In vitro* activity of doripenem tested against bacterial organisms commonly found in complicated intra-abdominal infection and complicated urinary tract infections.

Organism (# of isolates)	MIC (μg/mL)	
	MIC_{50}	MIC_{90}
Gram negative, aerobic		
Escherichia coli		
Non-ESBL (15,478)	≤0.06	≤0.06
ESBL producing (2,363)	≤0.06	≤0.06
Klebsiella pneumoniae		
Non-ESBL (5,387)	≤0.06	≤0.06
ESBL producing (2,444)	≤0.06	1.0
Proteus mirabilis		
Non-ESBL (1,766)	0.12	0.25
ESBL producing (129)	0.25	0.5
Pseudomonas aeruginosa (9,256)	0.5	8
Acinetobacter baumanii (2,982)	2	>8
Gram-positive, aerobic		
Enterococcus faecalis		
Vancomycin susceptible (8,412)	4.0	8.0
Vancomycin resistant (302)	8.0	>8.0
Enterococcus faecium (4233)	>8.0	>8.0
Viridans group streptococci (1,887)	≤0.06	0.25
Penicillin-Susceptible (1,337)	≤0.06	≤0.06
Penicillin-Resistant (550)	0.12	2.0
Streptococcus pneumoniae	≤0.06	0.5
Penicillin-Susceptible (6,598)	≤0.06	≤0.06
Penicillin Nonsusceptible (3,662)	0.25	1.0
Staphylococcus aureus		
Methicillin-susceptible (22,389)	≤0.06	≤0.06
Methicillin-resistant (16,515)	2.0	>8
Gram-negative, anaerobic		
Bacteroides caccae (16)	0.5	2
Bacteroides fragilis (198)	0.5	1.0
Bacteroides thetaiotaomicron (78)	0.5	1.0
Bacteroides uniformis (21)	0.5	1.0
Bacteroides vulgatus (31)	0.5	2

Adapted from Castanheira et al[4]; Fritsche et al[23]; Goldstein and Citron[24]; Mendes et al.[5]

Susceptibility Testing (EUCAST)]. In general, the doripenem susceptibility breakpoint is 1–2 dilutions lower than other carbapenems for most organisms, which is consistent with its lower approved dose (Table 2). Because of these differences, it is difficult to compare susceptibilities between compounds and their different dosage utilizations.

When observing the activity of doripenem against the US derived non-lactose fermenting Gram-negative organisms, doripenem inhibited 84 and 88% of *P. aeruginosa* at 1 and 2 μg/ml, respectively.[14,22] These percentages were slightly higher for doripenem compared with imipenem and meropenem; however, when the global surveillance was used, meropenem and imipenem showed comparable susceptibilities to doripenem at their respective breakpoints (~70%–80%).[4] Also noteworthy is doripenem's ability to retain activity against some imipenem-resistant *P. aeruginosa*. These potency differences do not carryover to *Acinetobacter* species. At 1 μg/ml, doripenem was only able to retain inhibition against a little less than 50% of *Acinetobacter* species worldwide, which was considerably less than the US surveillance of ~70%.[4,14] Imipenem and meropenem susceptibilities were approximately 15% higher than doripenem in the global surveillance[4] and similar to doripenem in the US surveillance. Again, these differences are largely reflective of currently different definitions for susceptibility.

The activity of doripenem against global Enterobacteriaceae isolates was more than ≥99.5% at both the US FDA and EUCAST MIC breakpoints of ≤0.5 μg/mL.[14] This activity was comparable with meropenem in each Enterobacteriaceae organism tested but was decidedly better than imipenem against the majority of organisms except *E. coli*, *Klebsiella* sp., and *Citrobacter* koseri.[5] When tested against multidrug resistant Enterobacteriaceae, doripenem had either equal or a slightly lower activity than the wild-type counterpart bacteria. This was particularly true against extended spectrum β-lactamase (ESBL) and de-repressed AmpC producing organisms. In a global surveillance study, ESBL producing *E. coli*, *Proteus mirabilis* and *Klebsiella oxytoca* and de-repressed AmpC producing *Enterobacter cloacae*, *C. freundii, S. marcescens, and Morganella morganii* phenotypes have had similar susceptibility to doripenem as their non-resistant phenotypes.[5] In contrast, when the susceptibility of ESBL-producing *K. pneumoniae* isolates were evaluated, the percentage inhibited was below 90%; this was nearly a 10% difference from the non ESBL-producing phenotype. One suggestion for the >4-fold MIC_{90} increase (ESBL-phenotype at 1 μg/mL and non-ESBL at ≤0.06 μg/mL) is the sporadic occurrence of isolates carrying carbapenemases, most notably the *Klebsiella* Producing Carbapenemase (KPC) that are common in the Mid-Atlantic region of the United States, and beginning to spread elsewhere in the world. Nevertheless, when doripenem MIC_{50} and MIC_{90} values of ESBL- and KPC-producing *K. pneumoniae* were compared with other carbapenems, doripenem demonstrated similar to slightly higher activity.[3]

In a global surveillance study that evaluated the *in vitro* activity of doripenem and 14 other antibiotics against a variety of staphylococci, streptococci, and

Table 2. Susceptibility/resistance breakpoints for anti-pseudomonal carbapenems as defined by CLSI, FDA, and EUCAST.

	CLSI/FDA		FDA	EUCAST		
	Imipenem	Meropenem	Doripenem	Doripenem	Imipenem	Meropenem
Enterobacteriaceae	≤4/>8	≤4/>8	≤0.5	≤1/>4	≤2/>8	≤2/>8
Pseudomonas sp.	≤4/>8	≤4/>8	≤2	≤1/>4	≤4/>8	≤2/>8
Acinetobacter sp.	≤4/>8	≤4/>8	≤1	≤1/>4	≤2/>8	≤2/>8
Enterococci	≤4/>8	≤4/>8	N/A	≤1/>4	≤4/>8	N/A
Streptococci	≤4/>8	≤4/>8	≤0.12	≤1/>1	≤2/>2	≤2/>8
Anaerobes	≤4/>8	≤4/>8	≤1	≤1/>1	<2/>8	≤2/>8

Adapted from Livermore.[22]
Abbreviations: CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration.

enterococci, doripenem exhibited a $MIC_{90} \leq 0.5$ µg/mL in all organisms except enterococci.[23] The MIC_{90} value for doripenem was ≥8 µg/mL for both *Enterococcus faecium* and *Enterococcus faecalis*, which is comparable with meropenem's MIC_{90} value for *E. faecalis* but a dilution lower than imipenem. Overall, among all the antibiotics evaluated, doripenem had one of highest potencies against the various staphylococci and streptococci tested. However, against MRSA or penicillin resistant streptococci, doripenem experienced a considerable decline in activity (between 3 to 8-fold increase at the MIC_{90}).[23]

When doripenem was evaluated against a variety of anaerobic organisms, it demonstrated activity to all except *Sutterella wadsworthensis* (MIC_{90} of 8 µg/mL).[24] Of the anaerobes tested, the MIC_{90} was no higher than 2 µg/mL. In particular, *Bacteriodes fragilis* was commonly found to have a doripenem MIC_{90} of ≤1 µg/mL;[24] therefore, the majority of *B. fragilis* isolates would have been defined as susceptible based on the established EUCAST and US FDA breakpoint of ≤1 µg/mL.[22] Additionally, the review by Goldstein and Citron showed the microbiological cure rates in cIAI at the established breakpoint of doripenem for *B. fragilis* infections were ~84%. For all the other *Bacteroides* isolates at the breakpoint, doripenem demonstrated microbiological cure rates between 86%–100%. These results, when compared with other carbapenems' activity against *B. fragilis*, were similar to meropenem and ertapenem; however, doripenem activity was slightly lower than imipenem. Contrary to these results, doripenem appeared to have slightly more *in vitro* activity against *Clostridium* spp., than the other carbapenems.

Mechanisms of resistance

Similar to other carbapenems, doripenem has a stable structure against most β-lactamase enzymes (e.g. AmpC and ESBL). However, doripenem's ability to resist hydrolysis were not shared against β-lactamases of Ambler class A (KPC and SME), C (VIM), and D (OXA).[3,5,14,25,26] The organisms commonly in possession of these carbapenemases are the non-lactose fermenting Gram-negative bacilli (i.e. *S. maltophilia*, *A. baumannii*, and less frequently *P. aeruginosa*) and more recently, *K. pneumonia* (Ambler class A and C). In some cases, the production of carbapenemases (e.g. IMP-1 or VIM) within certain Gram-negative rods may raise the MIC several fold but not high enough to be considered resistant.[25]

Other mechanisms (e.g. loss of porin channels and efflux overexpression) have also had a similar result on doripenem's susceptibility profile to that of meropenem.[27,28] For instance, Queenan and colleagues observed carbapenem resistance in *P. aeruginosa* isolates and doripenem typically needed both porin channel reductions along with AmpC elevation or efflux pump expression, in order to attain resistance. Meanwhile, imipenem was commonly found to exhibit resistance from the presence of either resistance mechanism. Similar to doripenem, meropenem demonstrated non-susceptibility but not resistance in *P. aeruginosa* isolates that exhibited a loss in outer membrane proteins (OprD).[29] When mutation frequencies were compared among the carbapenems with *P. aeruginosa* isolates, meropenem exhibited the highest frequency of mutant isolation; this incidentally happened to be OprD loss.[28] In the same study, doripenem had the tendency to inhibit mutant growth, even in the presence of sub-inhibitory concentrations from mutagenic agents (ciprofloxacin and ofloxacin). Although less common in Gram-negative bacilli,[29] another potential way to acquire resistance is through a reduction in penicillin-binding affinity. Often times, Gram-positive organisms (i.e. MRSA and Enterococcus sp.) have gained resistance through this mechanism by lowering the already low affinity at the target site (i.e. PBP 2a and PBP 5).[30]

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

Doripenem displays linear and dose proportional pharmacokinetics when dosed at a range of 250 mg to 1000 mg given over a 0.5, 1, or 4 h infusions.[31] During phase I studies, single or multiple doses (2 or 3 times daily) were used to total a maximum dose of 3000 mg per day (1000 mg every 8 h). The mean plasma pharmacokinetic parameters of a single 500 mg dose (1-h intravenous infusion) are displayed in Table 3. In the studies, the time in order to achieve maximum concentration (Tmax) immediately followed the end of infusion.[15,32,33] When compared to the mean Cmax after a 1-h infusion, the 4 h infusion was nearly one-third lower (~8 µg/mL) using the same 500 mg dose;[34]

Table 3. Mean pharmacokinetic parameters of healthy volunteers with normal renal function administered (e.g. a single dose of 500 mg over 1 h).

Parameter	Doripenem 500 mg
Cmax (μg/mL)	22–23
AUC0–∞ (μg∗h/mL)	31.8–38.7
Vd_{ss} (L)	16.8–24.8
CL (L/h)	13.2–16.0
CLR (L/h)	10.8–12.5
t1/2 (h)	1.1–1.3

Cirillo[32] (n = 8); Cirllo[33] (n = 6); Doribax[15] (n = 24).

this led to a mean AUC from time 0 to infinity for both infusions at ~34 μg∗h/mL.[34]

Based on a variety of different sources,[34–36] doripenem concentration-time profiles are best described by a 2-compartment model with zero order input and 1st order elimination. When doripenem was dosed over a course of 7–10 days, no accumulation was observed within each of the cohorts.[31] At steady state, doripenem 500 mg has displayed a median volume of distribution of 16.8 L in healthy volunteers; this is similar to the extracellular fluid volume of ~18 L.[15,33] Though research is limited to a few areas of the body (i.e. retroperitoneal fluid, peritoneal exudate, gall bladder, bile, and urine), doripenem has exhibited good tissue distribution with concentrations at or above the MICs of susceptible organisms.[15,33,37,38] Moreover, these concentrations appear to be mostly free drug, based on the 8.5% plasma protein binding exhibited by doripenem.[35] In a study by Ikawa et al, doripenem dosed at 500 mg over 0.5 h, had concentrations extensively and rapidly reach the peritoneal fluid in non-infected patients undergoing abdominal surgery. The results showed that 82% of doripenem (based on an AUC0-∞) reached the peritoneal fluid.[37]

Doripenem is eliminated renally by glomerular filtration and active tubular secretion with no indication of hepatic metabolism (i.e. CYP 450 enzymes).[15,33] When healthy males were administered a single 500 mg dose over 1-h, ~94% of doripenem was recovered in the urine over 24 h; the majority of doripenem was unchanged drug (~75%) with the remainder as the inactive metabolite, doripenem M-1 (~19%). Feces were also determined to be a route of elimination for active doripenem; however, it was very minimal at ≤1%.[33]

In studies that observed patients with various renal functions,[32,39] it was determined that doripenem dose regimens should be adjusted based on renal function below normal creatinine clearance (CrCL). This was due to the increased exposure observed in subjects with declining renal function due to decreased glomerular filtration. In two trials, single dosages of doripenem 500 mg (0.5 or 1h infusion) were used in subjects with various rates of renal function based on CrCL. Subjects with impaired renal function experienced a ~2 and ~8-fold increase in AUC0-∞ and ~2 to ~7-fold increased half-life when compared with the normal controls (CrCL ≥ 80 ml/min). When pre-dialysis and post-dialysis were compared to each other, pre-dialysis (doripenem dosed 2 h prior to 4 h dialysis) removed ~90% of doripenem, while, post-dialysis (doripenem dosed 1 h after dialysis) removed ~52% of doripenem. To our knowledge, the above mentioned hemodialysis studies are the only pharmacokinetic information on dialysis available. As a result, more information is needed in this area, specifically looking at dose effects on peritoneal dialysis and continuous renal replacement therapy (i.e. continuous veno-venous hemodialysis and continuous veno-venous hemodialysis-filtration).

When doripenem was evaluated in a variety of healthy subjects with varying characteristics (i.e. age, sex, and race), it was determined that dosage adjustments were not required.[15] However, among the various populations observed there were subtle differences in pharmacokinetic parameters. For instance, among the various races and age groups administered doripenem, only the Hispanic and geriatric populations was dissimilar when the mean CL was shown to be increased by >14% and mean AUC0-∞ was 49% higher, respectively.[15] Incidentally, the differences in the geriatric population were regarded to be attributable to age-related CrCL changes.

Pharmacodynamics

Based on various murine thigh infection models[40–42] and a time-kill study,[43] doripenem has demonstrated rapid bactericidal time-dependent activity against Gram-positive and Gram-negative organisms. The *in vitro* post-antibiotic effect of

doripenem varied within organisms tested between ~0.5 h in *E. coli* and *K. pneumoniae* and ~2.0 h in *S. aureus* and *P. aeruginosa*.[26,30]

In animal studies, free drug concentrations above the MIC ($fT > MIC$) for 20%–30% and 35%–45% of the dosing interval were required for bacteriostatic and maximal bactericidal activity, respectively. In one study,[40] doripenem at a static dose, 1-log kill (90% reduction in bacterial density) and 2-log kill (99% reduction in bacterial density) for *S. pneumoniae*, *S. aureus*, and various Gram-negative isolates required a $fT > MIC$ of ~30%, 36%, and 44%, respectively. A similar static exposure (23% $fT > MIC$) was required against carbapenemase (KPC)-producing Enterobacteriaceae.[41] In a study by Kim et al, human simulated exposures approximating a doripenem dose of 500 mg every 8 h using either a 1 h or 4 h infusion, should achieve equivalent bactericidal exposures at an MIC ≤ 2 μg/mL. At an MIC of 4 μg/mL, there appeared to be some variability but the 4 h infusion benefited against 2 of 4 isolates. At MICs beyond 4 (i.e. 8 and 16 μg/mL), neither the 1 h or 4 h infusions consistently prevented regrowth from ensuing in the *P. aeruginosa* isolates.

In various published in silico modeling studies, optimal dosing schemes to maximize doripenem exposures in blood,[35,36] blood + urine,[44] and blood + peritoneal fluid[38] were generated (Table 4). However, in two of the studies,[35,38] the population pharmacokinetic parameters were taken from healthy subjects with normal renal function (mean CrCL in both studies ≥ 80 ml/min) and it was thought that these simulated dosing regimens may not reflect populations with impaired renal function or infected patients. To correct for these limitations, two studies used subjects with varying renal function with and without concomitant infection.[36,44] These results were similar to healthy subject data; a dose at 500 mg every 8 h administered as 1 and 4 h infusions had a ≥90% probability of achieving a $fT > MIC$ of 35%–40% (PTA) for doripenem MICs of 1 μg/mL and 4 μg/mL, respectively. Finally, it should be noted that the use of 4-h infusions was a more effective way of increasing the drug exposures versus just increasing the dose regardless of the patient creatinine clearance.

In another pharmacodynamic study, urinary bactericidal titers (UBT) and area under the 24 h

Table 4. A comparison of pharmacokinetic/pharmacodynamic breakpoints for doripenem regimens in 4 different patient population studies.

Dori regimen	Time of infusion (hr)	Bhavnani 2005[a]	Ikawa 2008b (serum/PF)[b]	van Wart 2009[c]	Ikawa 2009[d]
		MIC breakpoint (μg/mL)			
0.25 g q12 h	1	N/A	N/A	≤4[#]	0.125/0.5*/1[#]
0.25 g q12 h	4	N/A	N/A	≤4[#]	N/A
0.25 g q8 h	1	0.5	0.5/1[§]	≤4*	0.5/1*/2[#]
0.25 g q8 h	4	N/A	2/2	≤4*	N/A
0.5 g q8 h	1	1	1/2[§]	≤1; ≤4[†]	1/2*/4[#]
0.5 g q8 h	4	4	4/4	≤4; ≤4[†]	4/4*/8[#]
1 g q12 h	4	4	N/A	≤8*	N/A
1 g q8 h	1	2[(?)]	2/4[§]	N/A	2/4*/8[#]
1 g q8 h	4	8	8/8	≤8	8/8*/16[#]

Notes: MIC Breakpoints are the highest MICs at which the probability of targets of 35 or 40% $fT > MIC$ were attained in plasma and/or peritoneal fluid was ≥90%.

[a]Healthy normal CrCL; [b]Non-infected normal CrCL in serum and peritoneal fluid; [c]Heterogeneous: Non-infected/infected with various levels of renal function; [d]Infected with various levels of renal function.

All MIC breakpoints based on normal renal function (CrCL of ≥80 μg/mL), unless otherwise denoted by:

[†]Mild (CrCl 50 to <80); *Moderate renal impairment (CrCL of 40 ml/min); [#]Severe renal impairment (CrCL of 20 ml/min); [§]0.5 h-infusion; [(?)]Assumed value based on information provided.

urinary bactericidal titers curve (AUBT) were used to determine the pharmacodynamic parameters of doripenem in urine.[45] Wagenlehner and colleagues used data and clinical isolates from Naber and colleagues' phase III clinical trial to determine and compare the UBT and AUBTs of doripenem and levofloxacin. Median results showed that doripenem had significantly higher UBT and AUBT than levofloxacin for 6 of 7 isolates at a range of 1.5 to 65,536 and 224 to 909,312 compared with 0 to 128 and 0 to 2,048. UBTs and AUBTs have correlated well with microbiological failures in the case of levofloxacin, suggesting a target attainment rate of UBTs of at least 100/24 hours. There was however no correlation of microbiological failures and UBTs and AUBTs in the case of doripenem. However in the majority of those cases non-resolution of the complicating urological factors could be attributed to failures.

Clinical Studies

Based on the available clinical trials data conducted in patients with cIAI[46,47] and cIAI (DORI-06),[11,48] doripenem received US FDA approval for the treatment of the aforementioned infections. Other clinical trials have been published for the treatment of ventilator associated pneumonia and nosocomial pneumonia; however, doripenem has not yet received approval for the treatment of either indication, although the results were promising.[49,50] In Europe, doripenem is approved for UTI, IAI, as well as hospital-acquired pneumonia.

Complicated intra-abdominal infections

Doripenem's efficacy and safety for the treatment of complicated intra-abdominal infections was determined in an international, multicenter, double-blinded, randomized controlled Phase III trial. In this study,[46] 476 adult patients (≥18 years of age) were randomized to receive doripenem 500 mg IV every 8 h as a 1 h infusion (n = 242) or meropenem 1000 mg every 8 h as a 3 to 5 min bolus (n = 233). In patients with a CrCl < 50 ml/min, dose adjustments were made in both treatment arms. In line with the difference in drug administration durations, patients also received a dummy placebo for control either before administering meropenem or after doripenem. Once a minimum of 9 doses were received and clinical improvements were observed, patients were allowed to switch from study drug to oral amoxicillin-clavulanate 875/125 mg bid for the remainder of the 5 to 14 day treatment course. The co-primary efficacy end points were the clinical cure rates of patients infected with ≥1 bacterial organism that were susceptible to both study drugs at the test of cure (TOC) visit (21–60 days post-completion of study drug therapy) and those patients identified with an infection regardless of susceptibility. The other endpoints included clinical cure rates in clinically (CE) and microbiologically evaluable (ME) patients at the end of study drug therapy, early follow-up (1 to 2 weeks after treatment), and TOC visit. Patients were stratified by region and within each region, by primary site of infection and APACHE II score (≤10 vs. >10). Clinical cure rates were 85.9% and 85.3% (0.6% difference; 95% confidence interval, −7.7% to 9.0%), respectively. In the microbiological modified intent to treat (mMITT) population, the clinical cure rates were at 77.9% and 78.9% (−1.0% difference; 95% CI, −9.7% to 7.7%) for doripenem and meropenem, respectively. In each of the outcomes observed, doripenem met non-inferiority (lower limit of the 2-sided 95% CI for the difference in the clinical cure rates was ≥−15%) to meropenem. Both study drugs were administered for an average of 6.6–6.8 days, while the oral formulation was continued for approximately 10.3–10.4 days. Among the three most common organisms found at baseline (*E. coli*, *B. fragilis* group, and virdans group streptococci), the doripenem and meropenem cohorts in the ME population exhibited favorable microbiological outcomes at 87.5% (91/104) versus 84.0% (84/100), 89.3% (67/75) versus 84.3% (75/89), and 92.6% (50/54) versus 85.4 (35/41), respectively.

In another cIAI trial, Solomkin and colleagues expanded the number of subjects by pooling the phase III study by Lucasti and colleagues with another similar clinical trial in cIAI by Malafaia.[51] In this study,[47] doripenem again demonstrated non-inferiority to meropenem at 84.6% versus 84.1% (+0.5% difference; 95% CI −5.5% to 6.4%) in the ME population, respectively. In the mMITT population, the clinical cure rates were 76.2% versus 77.3% (−1.1% difference; 95% CI −7.4% to 5.1%), respectively. Doripenem demonstrated numerically higher clinical cure rates compared with meropenem in patients with higher APACHE II scores, but this group was too small for a statistical assessment. Microbiological

cure rates in the ME population were again similar between doripenem and meropenem at 84.3% versus 84.5%, respectively. Microbiologial cure rates were also similar in the by-isolate assessment for *E. coli*, *B. fragilis* group, and virdans group streptococci.

Lower complicated urinary tract infections and pyelonephritis

During 2 phase III multi-center, clinical trials, doripenem 500 mg every 8 h infused over 1 h was administered to patients for at least 9 doses before the option of a treatment switch to oral levofloxacin 250 mg daily was offered for the remainder of the 10 day treatment course in clinically improving patients. Between the 2 trials, one study was a non-comparative single armed trial (DORI-06);[48] meanwhile, the trial by Naber et al[11] was double dummy designed comparing doripenem and levofloxacin 250 mg IV daily at a 1 h infusion. In both studies, non-inferiority was defined if the lower limit of the 2-sided 95% CI for the treatment difference (doripenem minus levofloxacin) with respect to microbiological cure (eradication of the baseline pathogen) at TOC (5–11 days in comparative study or 6–9 days in non-comparative study) in the ME and mMITT was ≥−10%. Among the two studies, a total of 795 patients were given ≥1 dose of doripenem (n = 423 in non-comparative and n = 372 in comparative), while 376 patients were given ≥1 dose of levofloxacin.

Demographic data of all cohorts in the ME at TOC population were similar with the majority of patients being Caucasian females at ~52 years of age. In the comparative study, an equal amount of patients had either pyelonephritis or cUTI, with ~8% of the ME population having bacteremia. Doripenem was non-inferior to levofloxacin in both studies, as shown by the respective agents microbiological cure rates in ME at 82.1% vs. 83.4% (−1.3% difference; 95% CI −8.0% to 5.5%) for the comparative study and 83.6% vs. 83.4% (+0.2% difference; 95% CI −6.6% to 7.0%) for non-comparative study. Doripenem also demonstrated non-inferiority to levofloxacin in the mMITT population for both studies with the microbiological cure rates at 79.2% vs. 78.2% (+1.0% difference; 95% CI −5.6% to 7.6%) for the comparative study and 82.5% vs. 78.2% (+4.3% difference; 95% CI −2.1% to 10.7%) for the non-comparative study, respectively. Clinical cure rates at TOC within each of the doripenem groups in comparative and non-comparative studies were 95.1% and 93.0%, respectively. Within the ME patients at TOC, the eradication rates of *E. coli* in the comparative and non-comparative study doripenem cohorts, were 84.4% and 92.0%, respectively; this is comparable to the levofloxacin group at 87.2%. Other organisms tested against doripenem and were mentioned as ME included *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, and *A. baumannii*.

Safety and Tolerability

Doripenem was well tolerated in phase I-III clinical studies. As shown in Figure 2, the adverse events reported in phase III trials were generally mild with most subjects commonly experiencing: headache, diarrhea, phlebitis, elevated hepatic enzymes, rash, nausea, and anemia.[11,15,48–50]

Serious adverse events, although limited were: hypersensitivity reactions, *Clostridium difficile* colitis, and fungal infections (i.e. vulvomycotic and oral candidasis).[15] Carbapenems have also been known to induce seizures[52] and lower seizure thresholds in animals.[52–54] In the phase III trials no patient experienced a seizure attributed to doripenem. Horiuchi and colleagues evaluated the convulsive activity and *in vitro* affinity to the GABA receptor of doripenem by using several animals in a variety of different experiments. Doripenem exhibited no convulsive activity when administered intravascularly or intraventricularly unlike many of the other antibiotics used for testing. Recently, a patient was treated with a 3 g per day dose of doripenem for a central nervous system infection (ventriculitis). In the case report, no adverse events were reported.[55] Despite all this information, post-marketing surveillance has reported seizure activity to exist with doripenem use.[15]

In pregnant women, doripenem has been given a rating of category B.[15] This is in response to doripenem not showing teratogenicity and not producing any adverse effects following its administration in pregnant animals. Unfortunately, there are no clinical trials with doripenem's use in pregnant woman, so it has been suggested that doripenem only be used when necessary. Among other specific populations, the use of doripenem in nursing mothers or pediatrics is not advised, mainly because doripenem has never been tested for safety in either population.[15] When doripenem was compared between subjects with varying degrees of renal function, no serious adverse

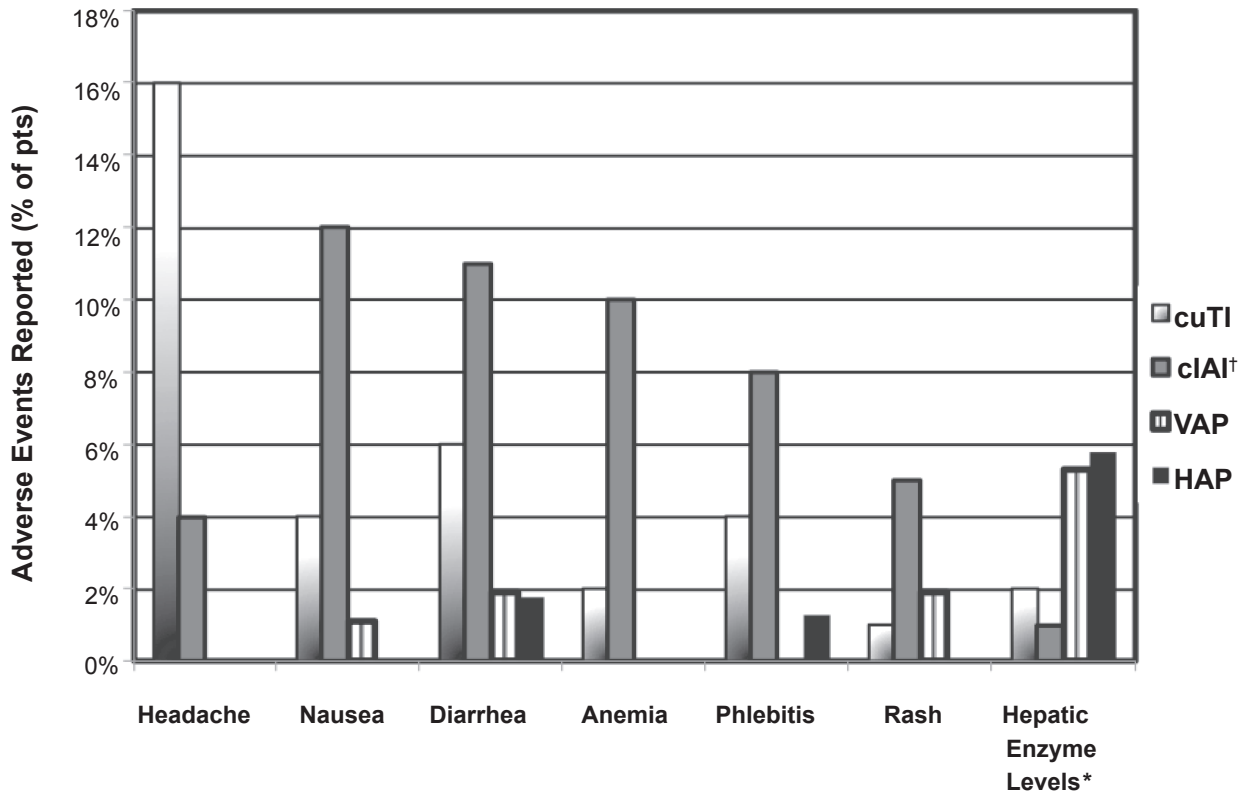

Figure 2. Bar graph representing the% patients reporting a drug-related adverse event to doripenem from five phase III clinical trials.
Adapted from: Chastre;[49] Doribax;[15] Réa-Neto.[50]
†Adverse reactions were reported from two phase III clinical trials.
*Includes reactions reported as abnormal: alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, and/or transaminases.

event was reported.[32] However, based on the fact that only 6–8 patients were used in each cohort and only 1–2 doses were administered, careful monitoring should still be taken in renal impaired patients.

Drug Interactions, Compatibility, Stability

When Horiuchi and colleagues[54] examined the concurrent use of doripenem with valproic acid, it was found that doripenem had no effects on valproic acid anti-convulsive activity. However, this observation contrast those found in other studies that noticed reduction in the plasma concentration of valproic acid when coadministered with doripenem.[56] Therefore, despite their documented findings, Horiuchi and colleagues[54] suggested that doripenem, like other carbapenems, not be coadministered with valproic acid in epileptic patients. Another agent suggested to not be coadministered with doripenem is probencid.[15] Probencid has been documented to interfere with active tubule secretion of doripenem. Consequentially, this interaction reduces the renal elimination of doripenem thus reducing the CL, which in turn would increase the systemic exposure of doripenem (i.e. Cmax and AUC).

When doripenem (diluted in normal saline and dextrose injection) during Y-site administration was tested against 82 other agents for physical compatibility, it was found that doripenem was compatible with 75 agents. Among these agents, 3 combined with doripenem in dextrose 5% and 7 drugs in normal saline resulted in precipitation after at least 4 hours of testing. These agents include: diazepam, potassium phosphate, and propofol in dextrose and normal saline and 4 different amphotericin B containing drugs (i.e. amphotericin B, cholesteryl sulfate complex, lipid complex, and liposomal) in normal saline.[57]

Unlike other carbapenems, doripenem can remain stable for as long as 12 h at room temperature conditions in normal saline.[21] This provides sufficient time to allow doripenem to be administered as an extended infusion, thus permitting greater exposures against organisms with higher MICs.

Place in Therapy

Within the last decade there have been higher occurrences reported of multi-drug resistant bacterial infections in various institutions both nationally,[14,58,59] and globally.[4,5,23,60] For instance, in certain regions of the United States, the percentage of *K. pneumoniae* carrying an ESBL, AmpC, or even worse a carbapenemase resistant enzyme is near 40%.[61] Moreover, in most areas of the U.S., the non-lactose fermenting Gram-negative bacilli (e.g. *P. aeruginosa* and *A. baumannii*) have left many institutions with few available antibiotic class options.[14,62] In light of this situation, various clinical guidelines incorporated broader spectrum agents (i.e. carbapenems) as a 1st line therapy.[8,62] For instance, Infectious Diseases Society of America has incorporated the carbapenems as 1st line regimens in nosocomial cIAI and nosocomial pneumonia (VAP included) along with cefepime, ceftazidime, and piperacillin/tazobactam plus an aminoglycoside or anti-pseudomonal fluoroquinolone. For the guidelines of cUTIs,[10] it was stated that highly resistant bacteria should be treated based on organism susceptibility. Given that data suggests delays in therapy for UTI do not adversely affect mortality to the same extent as other infections (e.g. bacteremia, nosocomial pneumonia), the use of carbapenems would be best suited as a directed therapy for a severe infection or population (e.g. critically-ill, health care associated, neutropenic, and transplant).

Doripenem is a potent carbapenem with many potential benefits and possible utilizations. However, because clinical trials are designed to determine non-inferiority, doripenem's role maybe best suited as a secondary agent in directed therapy for cUTI and cIAI, unless an institution's microbiological surveillance suggests otherwise. That being said, doripenem does possess the ability to inhibit mutant selection and often requires the need for two resistance mechanisms to result in clinical resistance. Other attributes that allow for doripenem to be a potential important agent for both cIAI and cUTI include its broad-spectrum activity, stability at room temperature, low protein binding, good tissue penetration, and mild adverse effects. As a result, doripenem is well suited, particularly as a prolonged infusion, for serious infections (e.g. nosocomial pneumonia) where multidrug resistant Gram-negatives might be suspected.

Conclusion

Doripenem is a carbapenem with potent *in vitro* activity against both Gram-positive and Gram-negative bacteria. In clinical trials, doripenem demonstrated non-inferiority to meropenem and levofloxacin in the treatment of cIAI and cUTI/pyelonephritis, thus resulting in FDA approval for these infections in the United States. Doripenem also performed admirably compared with piperacillin/tazobactam and imipenem for the treatment of nosocomial pneumonia, including VAP; at the time of writing, the FDA had required more information before approving doripenem for nosocomial pneumonia and ventilator associated pneumonia. With low protein binding rates, good tissue concentration, and low frequency for selecting out resistance, doripenem has many of the qualities that make a great antibiotic. Additionally, doripenem has excellent stability at room temperature and low rates of adverse events; subsequently, this allows for further enhancement of the drug's capabilities with the use of high dose extended infusion regimens.

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