Doripenem: A new carbapenem antibiotic a review of comparative antimicrobial and bactericidal activities

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Abstract: Doripenem is a new parental 1-β-methyl carbapenem which, unlike imipenem, does not require the addition of cilastatin on administration because of the protection afforded to doripenem by the 1-β-methyl component. It combines the in vitro activities of imipenem and ertapenem against gram-positive bacteria with the in vitro activity of meropenem against gram-negative bacteria. It has excellent bactericidal activity against *Streptococcus pneumoniae*. Carbapenem resistant mutants were selected with less frequency and lower minimum inhibitory concentrations (MICs) after exposure to doripenem than to imipenem or meropenem. High concentration levels of doripenem may be achieved in plasma. The half life of doripenem is higher than imipenem or meropenem. This new antibiotic has excellent in vitro activity and pharmacological properties. but how it may best be utilized still needs to be determined.

Keywords: MIC, mutant, MBC, pharmacokinetics, pharmacodynamics

Introduction

Antibiotic resistance is now part of the everyday vocabulary. It is a current problem and also one which will not reduce in importance, but rather increase. In order to ensure that we can tackle the daily challenges of bacterial infections we need antibiotics. However, the march of antibiotic resistance continues and increases with each passing year. It is unlikely and unrealistic to think therefore, that we will be able to quell the future challenges of antibiotic resistant bacteria with our current dwindling stocks of viable antibiotics. Unfortunately, the numbers of new antibiotics produced in the last 20 years has reduced considerably (Bosso 2005). To optimize the few new emerging antibiotics that are developed we must understand where they would best serve our needs in the fight against antibiotic resistant bacteria.

Multi-drug-resistant (MDR) bacteria contain many resistance mechanisms frequently including mobile resistance genes, which can spread resistance to classes of antibiotics within and between bacterial species. Identification of these bacteria and outbreaks caused by these MDR pathogens are increasing in frequency. Some of these bacteria, although infrequent to date, have increased their antibiotic resistant armory from MDR to pan-resistant, which leaves drug combination as the only viable treatment option. It is generally hoped that each new antibiotic launched will be capable of effectively inhibiting the increasing number of MDR bacteria, while also causing less side effects than those currently associated with antibiotics. This review will focus on a new antibiotic, doripenem, which is a member of the carbapenem family of antibiotics and will detail the comparative activities of this new antibiotic with a view to helping to identify the most effective use of this new antibiotic at a time of increasing antibiotic resistance.

Doripenem is a new parental 1-β-methyl carbapenem. The carbapenem class was initiated by the development of imipenem in 1985 and expanded by the inclusion of

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meropenem in 1996 and most recently by the addition of ertapenem. Carbapenem antibiotics are cell wall synthesis inhibitors and belong to the β-lactam family of antibiotics. Carbapenems differ from most β-lactam antibiotics by having stability to AmpC and Extended spectrum β-lactams (ESBL). They also do not select AmpC derepressed mutants from inducible populations. Doripenem, like meropenem, has stability against renal dehydropeptidases, which unlike imipenem does not require the addition of cilastatin on administration, as a result of the protection afforded by the 1-β-methyl component (Mori 1996). Doripenem has been developed to date for intravenous use. It has been described as having the favorable attributes of both imipenem and meropenem against both gram-positive and gram-negative bacteria. This review will discuss the published data on doripenem to date, which will either concur with or oppose this view.

Spectrum of antibiotic comparative activities and bactericidal activities

The activity of doripenem compared with other classes of antibiotics used widely to treat gram-positive and gram-negative bacteria has been measured most frequently in vitro by comparing the minimum inhibitory concentrations (MIC) of each of these antibiotics. Doripenem was second only to imipenem by 1 doubling dilution against the oxacillin-susceptible *Streptococcus aureus* isolates, Table 1 (Ge 2004). There was a marked increase in MIC_{90} for all carbapenems when tested against the oxacillin-resistant isolates. Oxacillin-resistant *S. aureus* are resistant to all β-lactam antibiotics. Doripenem had excellent activity against oxacillin-susceptible coagulase negative *S. aureus* but, as with the other carbapenems, had much reduced activity against the oxacillin-resistant isolates (Fritsche 2005). The MIC_{90} values of doripenem, imipenem and meropenem were the same for penicillin-susceptible and pencillin-resistant *Streptococcus pneumoniae* (Ge 2004). However, the ranking order of MIC_{90} values changed for the penicillin intermediate isolates to imipenem having the lowest MIC_{90} followed by doripenem, then meropenem and finally ertapenem with the highest MIC_{90}. Doripenem activity was equal to that of meropenem and imipenem for penicillin susceptible viridans *Streptococcus* but again the order of activity changed for the penicillin intermediate isolates; imipenem had the lowest MIC_{90} followed by doripenem and ertapenem with the highest MIC_{90} (Ge 2004; Jones 2004a).

The MIC_{90} value of doripenem was at least 1 doubling dilution lower than the other carbapenems against ceftazidime

Table 1 Comparative in vitro activity of doripenem

Bacteria	Antibiotic	MIC_{90} values (mg/L)
Staphylococcus aureus	Doripenem	0.06
Oxacillin susceptible	Imipenem	0.03
	Meropenem	0.12
	Ertapenem	0.25
Staphylococcus aureus	Doripenem	32
Oxacillin resistant	Imipenem	>32
	Meropenem	>32
	Ertapenem	>32
Coagulase negative	Doripenem	0.06
Staphylococcus oxacillin	Meropenem	0.12
susceptible	Ertapenem	0.5
Coagulase negative	Doripenem	16
Staphylococcus oxacillin	Imipenem	8
resistant	Meropenem	32
	Ertapene	>32
Enterococcus faecalis	Doripenem	8
	Imipenem	4
	Meropenem	16
	Ertapenem	16
Enterococcus faecium	Doripenem	>8
	Imipenem	>8
	Meropenem	>8
	Ertapenem	>8
Streptococcus pneumoniae	Doripenem	≤0.008
Penicillin susceptible	Imipenem	≤0.008
	Meropenem	≤0.008
	Ertapenem	< 0.015
Streptococcus pneumoniae	Doripenem	0.25
Penicillin intermediate	Imipenem	0.12
	Meropenem	0.5
	Ertapenem	1
Streptococcus pneumoniae	Doripenem	1
Penicillin resistant	Imipenem	1
	Meropenem	1
	Ertapenem	2
Viridans Streptococcus	Doripenem	0.06
Penicillin susceptible	Imipenem	0.06
	Meropenem	0.06
	Ertapenem	0.25
Viridans Streptococcus	Doripenem	0.5
Penicillin intermediate	Imipenem	0.12
	Ertapenem	1
Viridans Streptococcus	Doripenem	4
Penicillin resistant	Imipenem	2
	Meropenem	4
	Ertapenem	8
Escherichia coli	Doripenem	0.03
ESBL negative	Imipenem	0.5
	Meropenem	≤0.015
	Ertapenem	≤0.015
Escherichia coli	Doripenem	0.06
ESBL positive	Imipenem	0.5
	Meropenem	0.06
	Ertapenem	0.5
Klebsiella species	Doripenem	0.06
ESBL negative	Imipenem	≤0.5
	Meropenem	0.03

(*Continued*)

Table 1 *(Continued)*

Bacteria	Antibiotic	MIC_{90} values (mg/L)
	Ertapenem	≤0.06
Klebsiella species	Doripenem	0.12
ESBL positive	Imipenem	≤0.5
	Meropenem	0.12
	Ertapenem	0.5
Klebsiella pneumoniae	Doripenem	0.12
ESBL negative	Imipenem	1
	Meropenem	0.03
	Ertapenem	≤0.015
Klebsiella pneumoniae	Doripenem	0.12
ESBL positive	Imipenem	1
	Meropenem	0.06
	Ertapenem	0.25
Enterobacter aerogenes	Doripenem	0.12
Ceftazidime susceptible	Imipenem	2
	Meropenem	0.06
	Ertapenem	0.06
Enterobacter aerogenes	Doripenem	0.12
Ceftazidime non-susceptible	Imipenem	1
	Meropenem	0.12
	Ertapenem	0.5
Enterobacter cloacae	Doripenem	0.06
Ceftazidime susceptible	Imipenem	2
	Meropenem	0.06
	Ertapenem	0.06
Enterobacter cloacae	Doripenem	0.25
Ceftazidime non-susceptible	Imipenem	1
	Meropenem	0.25
	Ertapenem	1
Acinetobacter spp	Doripenem	4
	Imipenem	2
	Meropenem	8
	Ertapenem	>8
Acinetobacter baumannii	Doripenem	>32
Carbapenem resistant	Imipenem	>32
	Meropenem	>32
	Ertapenem	>32
Acinetobacter baumannii	Doripenem	1
Ceftazidime susceptible	Imipenem	0.25
	Meropenem	1
	Ertapenem	8
Acinetobacter baumannii	Doripenem	>16
Ceftazidime resistant	Imipenem	8
	Meropenem	16
	Ertapenem	>16
Citrobacter freundii	Doripenem	0.03
Ceftazidime susceptible	Imipenem	1
	Meropenem	0.03
	Ertapenem	≤0.015
Citrobacter freundii	Doripenem	0.12
Ceftazidime non-susceptible	Imipenem	1
	Meropenem	0.06
	Ertapenem	0.5
Pseudomonas aeruginosa	Doripenem	0.05
	Imipenem	2
Carbapenem susceptible	Meropenem	1
	Ertapenem	16
Pseudomonas aeruginosat	Doripenem	8
Carbapenem resistan	Imipenem	32
	Meropenem	16
Pseudomonas aeruginosa	Doripenem	2
Cystic Fibrosis isolates	Imipenem	16
Burkholderia cepacia	Doripenem	8
	Imipenem	8
	Meropenem	4
	Ertapenem	8
Aeromonas	Doripenem	1
	Imipenem	2
	Meropenem	1
	Ertapenem	1
Stenotrophomonas maltophilia	Doripenem	>8
	Imipenem	>8
	Meropenem	>8
	Ertapenem	>8

susceptible or resistant *Enterobacter aerogenes* and *Enterobacter cloacae* (Ge 2004). Doripenem and meropenem had the lowest MIC_{90}s against ESBL producing *Escherichia coli* and *Klebsiella* isolates (Ge 2004; Fritsche 2005). Whereas doripenem had the highest MIC_{90} for the 1107 *Klebsiella* species tested with varying susceptibility profiles (Fritsche 2005). The MIC_{90}s of doripenem, ertapenem and meropenem were the same against *Aeromonas* species tested (Fritsche 2005).

Doripenem also had the highest activity against *Pseudomonas aeruginosa* isolated from cystic fibrosis patients or non-cystic fibrosis patients (Tsuji 1998; Jones 2004a; Traczewski 2006). *Pseudomonas aeruginosa* isolates from cystic fibrosis patients are normally more mucoid and generally more resistant than their non cystic fibrosis counterparts. It also had the highest activity against both carbapenem susceptible and resistant isolates of *P. aeruginosa* (Tsuji 1998; Jones 2004b). Against 24 carbapenem, resistant isolates of *Acinetobacter baumannii* at least 12 had doripenem MICs of 8 mg/L or less, the highest activity of the 4 carbapenems tested (Jones 2004b). Five isolates were susceptible to doripenem, 4 susceptible to imipenem and 1 susceptible to meropenem. Therefore, doripenem had the ability to be active against the imipenem resistance mechanism used by 1 isolate and for 4 isolates doripenem superseded the activity of meropenem.

There have been few studies on the bactericidal efficacy of doripenem. Killing curves have indicated that the Minimum Bactericidal Concentration (MBC) of doripenem ranged from 2-fold to 8-fold greater than the MIC. The bactericidal activity of doripenem was observed at 4 X and 8 X MIC for *S. aureus,*

E. faecalis, S. pneumoniae, E. coli and *K. pneumoniae*. The results of this study suggested that doripenem killing was as frequent at 2X MIC as 8X MIC against *S. pneumoniae* ATCC 49619 and thus was time rather than concentration dependent. Results for *P. aeruginosa* showed regrowth of the organism at 2X and 4X MIC but not at 8X MIC, which could be due to drug inactivation or indicate that bactericidal activity of doripenem against *P. aeruginosa* is not as efficient as with other bacteria (Jones 2004a). Thus more frequent dosing or a higher dose is required for *P. aeruginosa* infections.

Mutant selection

Transconjugant isolates of *E. coli* containing OXA, SHV, TEM, NMC and IMP resistance β-lactamases were generated (Mushtaq 2004a). Doripenem MICs for these isolates were comparable to or lower than the other 3 carbapenems; meropenem, imipenem and ertapenem and were also similar to the MIC against *E. coli* lacking the plasmid encoded resistance genes. Therefore, these resistance mechanisms alone do not confer resistance to doripenem. The MIC of doripenem was investigated for 2 *K. pneumoniae* variants of a single strain which were IMP positive but lacked an outer membrane porin (Mushtaq 2004a). The MIC of doripenem for the IMP-1 positive, porin negative isolate was the lowest of the 4 carbapenems and was the same as the 4 carbapenems for the IMP-1 positive, porin positive variant. However, the MICs of the 4 carbapenems were higher for the variant without the porin than the variant with the porin, suggesting that all 4 carbapenems rely on the same porin to enter the bacterial cell, although perhaps to different extents.

Mutant *P. aeruginosa* isolates were generated by selection on agar containing doripenem (Mushtaq 2004b). The results of these experiments elucidated that there were fewer mutants produced from exposure to doripenem than the other carbapenems and the mutants which were generated had lower MICs for doripenem than for the other carbapenems. The mutants selected on doripenem, which were non-susceptible to doripenem, were co-resistant to the other carbapenems. Co-resistance to non-carbapenem β-lactams was observed within most multi-step mutants generated from selection with doripenem or meropenem, which implies that efflux as well as loss of the OprD porin has a role in these resistant isolates. However, imipenem mainly selected mutants with resistance only to carbapenems, which would indicate that resistance is due only to loss of the OprD porin. This is worrying as it suggests that cross-resistance from doripenem to the other carbapenems, especially meropenem, could occur due to efflux upregulation and loss of the OprD porin in the clinical setting and vice versa. It is therefore unlikely that doripenem would have activity against meropenem resistant isolates.

Doripenem had excellent activity against isogenic strains of *P. aeruginosa*, which contained the OprD porin, regardless of AmpC production, in line with all carbapenems (Mushtaq 2004b). The influence of AmpC only affected the carbapenems in isolates lacking the OprD porin. The isolates overexpressing AmpC were non-susceptible to the carbapenems but those with low level or background levels of AmpC production were susceptible to all carbapenems. Therefore, doripenem performed in the typical manner of the carbapenems against the OprD negative isolates but when the OprD porin was present performed at a higher level. This result suggests that doripenem enters the bacterial cell at a faster rate than the other carbapenems through the OprD porin.

Similar to imipenem and meropenem, doripenem had activity against a range of TEM, PSE, PER, NPS and some OXA positive isolates of *P. aeruginosa* (Mushtaq 2004b). However, doripenem was weaker against the OXA-10 high producer isolate. Perhaps the mutation present in this OXA-10 enzyme, which differentiates it from the other OXA enzymes, enhances the activity of this enzyme to target specifically the modified carbapenem structure of doripenem. Clinical isolates of *P. aeruginosa* with various VIM and IMP metallo-β-lactamases were resistant to all 4 carbapenems. However, a Canadian isolate containing the IMP-7 metallo-β-lactamase was susceptible to doripenem only. Perhaps the specific structure or activity profile of this enzyme prevents it from interacting with the modified carbapenem structure of doripenem. If this is the case then doripenem could be used to specifically remove or reduce the resistance problem caused by these enzymes. The potential is therefore present to produce a carbapenem, which has activity against the metallo-β-lactamases. Further study into which resistance enzymes are particularly susceptible to doripenem and how this occurs is required. The roles of efflux and the OprD porin were not studied in these isolates but could also affect susceptibility to certain carbapenems.

Pharmacokinetics, pharmacodynamics and in vivo efficacy

In vivo experiments with doripenem have been performed both in mice and rats. Results of the mice experiments indicated that doripenem had approximately the same activity as imipenem and meropenem or slightly enhanced activity

against *S. pneumoniae*, *S. aureus*, *E. coli* and *P. aeruginosa* (Tsuji 1998). Doripenem also had the advantage of reaching high levels in the plasma of mice. In the rat experiments the bacteriological activity of doripenem was higher than that of imipenem/cilastatin against *E. coli* and *Bacteroides fragilis* polymicrobial infections (Mikamo 2000).

The MIC values to classify isolates as susceptible and resistant to doripenem suggested by Bhavnani et al (2003), Thye et al (2003) and Andes et al (2003) are susceptible $\leq$4 mg/L and resistant $\geq$16 mg/L, with intermediate being inferred as 8 mg/L. These values were derived by applying the pharmacokinetic (PK) and pharmacodynamic (PD) calculations from Monte Carlo simulations and in vivo studies in mice (Bhavnani 2003; Thye 2003; Andes 2003).

The time for which the doripenem concentration exceeds the MIC (T $>$ MIC), was found to be the PK-PD that correlated best with change in bacterial count ($\log_{10}$CFU/thigh mouse) for *S. pneumoniae*, *S. aureus* and *K. pneumoniae* (Andes 2003). This model utilized an estimated terminal half-life of doripenem of approximately 59.4 minutes based on a previous study in human subjects (Bhavnani et al 2005). As the range of MICs of doripenem against a diverse range of bacterial species is wide, the PK-PD target evaluation was found to be best studied within the MIC range of $\leq$1 mg/L to 2 or 8 mg/L. Using this regimen, in 24 healthy subjects between 18 and 65 years of age, Bhavnani et al established that by varying the length of doripenem infusion the same dosing regimen should allow for the effective treatment of pathogens with various MICs with little or no increase in drug exposure (Bhavnani 2005). However, due to the few studies in this area further research is required before this can be recommended.

Tsuji et al using a mouse model of systemic infection, identified a shorter half-life for doripenem of 17.7 minutes (Tsuji 1998). This half life was shorter than imipenem (18.5 minutes) but longer than meropenem (10.2 minutes). The variation in half life times between this study and that of Bhavnani et al could be due to the different models used or the fact that healthy subjects rather than infected subjects were used in the Bhavnani et al study and therefore the uptake of drug was less than in the infected mice models. The maximum concentration of doripenem achieved in the plasma was higher than that achieved by imipenem and similar to that of meropenem.

Conclusion

Many studies detailed in this review identified that doripenem had the in vitro activity to match imipenem or ertapenem against gram-positive bacteria and meropenem against gram-negative bacteria. The bacteria which doripenem had the greatest activity against, compared with other carbapenems, were oxacillin-susceptible or resistant *S. aureus* and coagulase negative *Staphylococcus*, *E. faecalis* and *E. faecium*, penicillin-susceptible or penicillin-resistant *S. pneumoniae*, viridans *Streptococcus*, ESBL-producing *E. coli* and *Klebsiella* species, ceftazidime non-susceptible *Enterobacter aerogenes* and *Enterobacter cloacae*, *Aeromonas*, carbapenem-resistant *Acinetobacter baumannii* and *P. aeruginosa*, carbapenem-susceptible *P. aeruginosa* and *P. aeruginosa* from cystic fibrosis patients. This list of both gram-positive and gram-negative bacteria demonstrates that doripenem has a wide range of activity. However, it did not have activity against the ever increasing number of metallo-β-lactamase-producing bacteria or those containing the plasmid mediated carbapenem-resistant genes. There is a great need for an antibiotic with high activity against such organisms; doripenem does not appear to be such an antibiotic. It also appears that loss of the OprD porin and efflux may effect the activity of doripenem.

As doripenem does not require the addition of cilastatin there is decreased seizure potential compared to imipenem. The extended dosing interval provides greater time above MIC.

The results to date indicate that doripenem is a broad spectrum antibiotic which combines the positive qualities of both imipenem and meropenem and has slightly enhanced activity to both, but it does not out perform these drugs to such an extent that either imipenem or meropenem will be consigned to the shelf. In its own right doripenem has excellent activity but where it fits into the current antibiotic prescribing practices still remains to be seen.

The question, therefore, that remains to be answered is the same as those that occurred when new antibiotics from other classes were introduced; will this antibiotic improve the antibiotic armory currently available to us or will it reduce the effectiveness of one of the few remaining effective classes? The only way we will know the answer to this question is to fully understand how resistance will develop to doripenem and if doripenem in turn can select for resistance to the other members of the carbapenem class. Therefore, caution is required in the first instance until we can answer these questions. All early indications show that doripenem is an antibiotic that is effective against gram-positive and gram-negative bacteria. However, the specific details of when and where this antibiotic should be used are still to be decided.

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