Doripenem

An Early Look at a Carbapenem Not Yet Approved for Pediatrics

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Key Words: carbapenem, imipenem, meropenem, ertapenem, doripenem

Doripenem (Doribax, Ortho McNeil, Jansen Pharmaceuticals) is the most recent addition to the carbapenems, a group of synthetic antibiotics structurally related to β-lactam agents which include imipenem, meropenem, and ertapenem. The importance of these agents has been heightened by the exception of the older agents, imipenem and meropenem, the pharmacologic characteristics of these agents in children and neonates have received relatively meager attention. Therefore, this review will focus on the in vitro and comparative activity of Doripenem with that of the other agents.

PHARMACOLOGY

Pharmacologic and postlicensure studies of doripenem in children has been initiated. The package insert clearly states that the “safety and efficacy in pediatrics has not been studied.”3 Doripenem intended for use in adults is provided in single-use vial as 500 mg for intravenous use. The dosage recommendation for persons equal to, or greater than, 18 years of age is 250 mg every 8 hours with infusion of the dose to be given in one hour. Significant dosage reductions are recommended for persons with reduced creatinine clearance to 250 mg every 8 hours and 250 mg every 12 hours for persons with creatinine clearance of ≥30 to 50 and >10 to <30 mL/min, respectively. Approximately 50% of the dose is removed during 4 hours of hemodialysis. Mean plasma concentration in adults following a 500 mg infusion is 23 mcg/mL. Doripenem has high penetration in peritoneal fluids and is primarily excreted by active glomerular filtration and tubular secretion. Approximately 70% of a dose is excreted unchanged in urine and 15% as the “ring-opened” metabolite; this metabolite forms as a result of urinary dehydropeptidase I, similar, but to a lesser degree than of imipenem.

Reported adverse reactions include those similar to other related compounds, including hypersensitivity reactions, including anaphylaxis, and toxic epidermal necrolysis (Steven, Johnson syndrome), as well as mild to moderate phlebitis, headache, nausea, diarrhea, and rash. In addition, neutropenia and leucopenia have been reported. Other clinical and laboratory abnormalities noted during treatment course have included mild elevations in ALT and AST, mild thrombocytopenia, elevated eosinophil counts, and diarrhea. The package insert includes a precautions for the occurrence of mild to severe (including fatalities) Clostridium difficile associated colitis or diarrhea. Because of the occurrence of moderately severe pneumonitis with the aerosolized administration of doripenem, this route is listed as a contraindicated.

The coadministration of doripenem with sodium valproate or valproic acid reduces the serum concentration of valproic acid. Reductions of the serum level of valproic acid below the therapeutic level (50–100 mcg/mL) occurs within 12 hours of initiating therapy.3 Case reports of a similar...
but imipenem was found to produce seizure discharges caused by a lowering of a gamma-aminobutyric acid receptor antagonist. These studies, doripenem and meropenem induce seizure discharges caused by a reduction in valproic acid has been noted with other carbapenems. Therefore, patients with seizure disorders controlled with valproic acid are at an increased risk of breakthrough seizures, during the administration of doripenem. However, in experimental animal studies conducted in the 1990s carbapenems induce seizure discharges caused by a lowering of a gamma-aminobutyric acid receptor antagonist.5 These studies, doripenem was found to be free of any predisposing electrical features of seizures, as was meropenem, but imipenem was found to produce seizure spikes at relatively low concentrations.

**CLINICAL UTILITY OF DORIPENEM IN ADULTS**

The FDA has approved doripenem for 2 indications—complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis.6 For both of these infections, a wide variety of aerobic nonfermentative Gram-negative rods (including Acinetobacter and Pseudomonas) are listed as specific agents for which the antibiotic is effective in these conditions. However, indications are listed for the treatment of infections due to even wider variety of microorganisms including facultative Gram-negative bacteria, facultative Gram-positive bacteria, and a variety of anaerobic organisms. These later indications are based on in vitro activity.

Efficacy in intra-abdominal infections (perforated viscus, peritonitis, abscess, and cholecystitis) was studied against meropenem in a phase III study in 946 adults in standard dosages given previously3,6; doripenem was found to be noninferior to meropenem in clinical cure rate and microbiological eradication of organisms. Treatment of complicated urinary tract infections and pyelonephritis with doripenem was compared with 10 to 14 days of treatment with levofloxacin in approximately 1171 randomized adults; doripenem was again found to noninferior to the comparator drug Levaquin.3

Phase III and postlicensure studies have been completed on patients with nosocomial pneumonia or ventilator associated pneumonia in patients treated with doripenem or piperacillin/tazobactam, both administered in standard adult dosages.7,8 Cure rates of nosocomial pneumonia were 81.3% for doripenem compared with 79.8% for piperacillin/tazobactam. Against ventilator associated pneumonias comparing doripenem with imipenem reported cure rates were 68.3% and 64.8%, respectively. However, cure rates against ventilator associated pneumonias caused by Pseudomonas aeruginosa were 65% for doripenem versus 36% for imipenem.

No children were included in phase III trials of doripenem. Neither pharmacologic, safety, nor efficacy data against infections in children have been reported. However, multiinstitutional efficacy and pharmacology postlicensure trials have been initiated in children.

### TABLE 1. Percent Antimicrobial Susceptibility Against Pseudomonas aeruginosa in TRUST 10 and 11 (2006–2007)

<table>
<thead>
<tr>
<th>Antimicrobial Agent Isolates (Laboratories)</th>
<th>TRUST 10, 2006 712 (37)</th>
<th>TRUST 11, 2007 868 (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>85.1 (82.6)</td>
<td>82.6 (84.1)</td>
</tr>
<tr>
<td>Doripenem</td>
<td>88.8 (87.4)</td>
<td>89.1 (89.8)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>91.2 (89.1)</td>
<td>90.9 (89.8)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>90.9 (89.8)</td>
<td>25.8 (23.7)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>88.8 (88.3)</td>
<td>87.2 (86.7)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>87.6 (87.8)</td>
<td>87.2 (86.7)</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>87.6 (87.8)</td>
<td>87.2 (86.7)</td>
</tr>
</tbody>
</table>

### TABLE 2. Representative MIC90 Antimicrobial Activity of Carbapenems Against Selected Gram-Positive and Gram-Negative Bacteria

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Doripenem</th>
<th>Meropenem</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>0.03</td>
<td>0.016–0.03</td>
<td>0.12–0.25</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>0.06–0.12</td>
<td>0.03–0.12</td>
<td>0.25–0.50</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0.50</td>
<td>0.12</td>
<td>4.0</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>0.03–0.06</td>
<td>0.03–0.06</td>
<td>0.50–1.0</td>
</tr>
<tr>
<td>E. cloaca</td>
<td>0.06</td>
<td>0.06</td>
<td>0.50</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>0.25–0.50</td>
<td>0.12</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>1.0–2.0</td>
<td>2.0–4.0</td>
<td>2.0–8.0</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Burkholderia</td>
<td>8.0</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>0.5</td>
<td>0.25</td>
<td>4.0</td>
</tr>
<tr>
<td>S. pneumoniae PanS</td>
<td>0.008</td>
<td>0.016</td>
<td>0.008</td>
</tr>
<tr>
<td>S. pneumoniae PenR</td>
<td>0.50</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>S. aureus, MSSA</td>
<td>0.06</td>
<td>0.12</td>
<td>0.16–0.03</td>
</tr>
<tr>
<td>S. aureus, MRSA</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>4.0</td>
<td>8.0</td>
<td>1.0</td>
</tr>
<tr>
<td>E. faecium</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
</tbody>
</table>

In vitro activity of doripenem

*Pseudomonas* organisms have played a critical role in complicated urinary tract infections, intra-abdominal infections, and nosocomial pneumonias. Therefore, comparative in vitro studies of doripenem have focused on the relatively potency compared the 2 other carbapenems with activity against *Pseudomonas aeruginosa*, imipenem, and meropenem. Ertapenem, has no activity against *Pseudomonas* organisms and has not been examined in most recent studies.

Table 1 compares the activity of these 3 carbapenems and other antipseudomonal antibiotics in the Tracking Resistance in the US Today (TRUST) 10 and 11 studies.9,10 Activity of doripenem against *Pseudomonas* isolates has been consistently greater than meropenem (approximately 2 fold greater on a weight basis) and strikingly greater than imipenem (approximately 5–10 fold greater on a weight basis). However, since the pharmacokinetics of doripenem and meropenem are similar, it is not clear that the slight to moderate advantage in inhibitory activity of doripenem is clinically significant. Indeed to date, clinical comparisons of the 2 agents have had similar outcomes.

Table 2 compares the activity of doripenem to that of meropenem and imipenem against selected Gram-negative and positive isolates. In general, based on inhibitory concentrations to which 90% of isolates are susceptible (MIC90), meropenem is slightly more active than doripenem against Gram-negative pathogens other than *Pseudomonas* and also more active against β-lactam susceptible Gram-positive pathogens. Again, the clinical significance of these small differences is not known. Against ESBL producing *Escherichia coli* and *Klebsiella pneumoniae*, the mean MIC90 raises a single dilution (eg, 0.3 μg/mL for doripenem or meropenem to 0.6 μg/mL for ESBL producers). In the TRUST 11, *Acinetobacter* species were consistently resistant to all 3 carbapenems.
with MIC\textsubscript{90} consistently >32 µg/mL, as were MIC\textsubscript{90} against Stenotrophomonas maltophilia and Enterococcus faecium.

Similar to other carbapenems, doripenem has considerable and consistent in vitro activity against anaerobic pathogens, its notable success against intra-abdominal infections undoubtedly confirms this activity in part. However the MIC\textsubscript{90} against Bacteroides fragilis (1.0 µg/mL), B. thetaiotaomicron (0.5 µg/mL), Prevotella species (0.125 µg/mL), F. nucleatum (0.03 µg/mL), and C. perfringens (0.03 µg/mL) are comparable to those of imipenem and meropenem and all 3 have relatively poor inhibitory activity against C. difficile with MIC\textsubscript{90} of ≥4 to 8 µg/mL.

INHIBITION OF RESISTANT MUTANT FORMATION

Perhaps the most controversial topic of in vitro activity of doripenem is possible suppression of antibiotic resistant mutants of Pseudomonas isolate.\textsuperscript{11–13} Early studies of comparative activity of doripenem against ertapenem, imipenem, and meropenem found that selection of resistant mutants was much less likely with doripenem, regardless of the mechanism of resistant (eg, efflux mechanisms, AmpC, and porin expressions or Class A or D β-lactamases or metallo-β-lactamase production).\textsuperscript{11} Subsequent studies have generally confirmed these early observations.\textsuperscript{12,13} Some studies have suggested that the exposure to fluoroquinolones enhances the expression of porin-mediated resistant in Pseudomonas and that this resistance is much more likely in the presence of meropenem than doripenem.\textsuperscript{13} However, since these studies have all been in controlled in vitro conditions, it remains to be seen what the true clinical significance of these findings will be when doripenem is widely dispersed as a therapeutic agent.

SUMMARY

Doripenem currently demonstrates consistent activity against most anaerobes with the exception of C. difficile, beta-lactam susceptible and good activity against Gram-positive organisms such as methicillin-sensitive Staphylococcus aureus and S. pneumoniae, but with relatively poor activity against MRSA strains. The broad activity against aerobic Gram-negative rods, including most ESBL producing E. coli and Klebsiella pneumoniae coupled with a consistently enhance activity against Pseudomonas aeruginosa may possibly make it a useful tool for nosocomial infections or those infections in which there is a prominent role for enteric and nonfermentative Gram-negative rods. However, until efficacy, safety, and pediatric pharmacology are known, meropenem offers a carbapenem with many of the features of doripenem. The question of whether doripenem will suppress the emergence of resistant Pseudomonas isolates during treatment or within the nosocomial environment remains an open question.

REFERENCES