

Daptomycin: A New Antibiotic with Gram-Positive Activity

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Daptomycin (Cubicin™, Cubist Pharmaceuticals) is the first antibiotic in the new cyclic lipopeptide class. It is bactericidal and works by binding to the bacterial cell membrane and causing a loss of membrane potential. The result is cell death due to the end of the production of DNA and RNA and the termination of protein synthesis.

PHARMACOLOGY/PHARMACOKINETICS

Daptomycin is active *in vitro* against a variety of gram-positive microorganisms. This includes some gram-positive isolates resistant to methicillin, vancomycin and linezolid. The *in vitro* activity of daptomycin is bactericidal and concentration-dependent.

Daptomycin is administered as a 30-minute intravenous infusion. Daptomycin is 92% reversibly protein bound. The protein binding is concentration-independent. The drug has an approximate volume of distribution of 0.09 liters per kilogram. Daptomycin does not inhibit or induce cytochrome P450 isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. The elimination half-life and the plasma clearance are approximately 9 hours and 8.2 mL/hr/kg, respectively. The major route of elimination for daptomycin is the kidney with approximately 50% of the administered dose being excreted unchanged in 24 hours. In patients with creatinine clearance values less than 30 mL/min, the area-under-the-curve (AUC) is increased by a factor of two. In patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), there is an increase in AUC of a factor of three. A dosage reduction is recommended in patients with creatinine clearances less than 30 mL/min, on hemodialysis or on CAPD. In patients undergoing hemodialysis, daptomycin should be given post-hemodialysis. No dosage adjustment based on gender or age is recommended. Dosage adjustment based on hepatic insufficiency does not appear to be necessary. The pharmacokinetics of daptomycin in children are unknown.^{2,3}

MICROBIOLOGY/RESISTANCE

Gram-positive cocci

Several *in vitro* studies have been done to evaluate the activity of daptomycin against a variety of organisms (see Table 1). Wise and associates demonstrated *in vitro* that the amount of calcium in a culture medium affected the activity of daptomycin.⁴ In methicillin-resistant *Staphylococcus aureus*, the MIC₉₀ is 8 mg/L

Summary

Indications. Daptomycin (Cubicin™, Cubist Pharmaceuticals) is indicated for the treatment of complicated skin and skin structure infections due to various gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible only).¹

Monitoring parameters. Therapeutic monitoring parameters include cultures and sensitivities, WBC with differential and temperature. Toxic monitoring parameters include CBC, serum chemistry, vital signs for anaphylaxis, liver function tests, CPK levels, and monitoring for muscle weakness, rash, or gastrointestinal disturbances.

Dose. The recommended dose of daptomycin is 4 mg/kg intravenously once every 24 hours for 7 to 14 days. Intravenous infusions should be administered over 30 minutes.

Pediatrics. Safety and effectiveness in pediatric patients have not been established.

Geriatrics. In phase III clinical trials, a decrease in effectiveness and an increase in emergent adverse events were observed in geriatric patients 65 or older when compared to patients younger than 65. In addition, elderly patients may have decreased renal function, and the dose of daptomycin should be adjusted in patients with renal insufficiency.

Pregnancy. Category B

Renal insufficiency. No dose adjustment is needed for patients with a creatinine clearance of at least 30 mL/min. Patients with a creatinine clearance of less than 30 mL/min should receive 4 mg/kg every 48 hours.

Cost. AWP for a 500-milligram vial of daptomycin is \$168. The cost of a seven-day course of therapy for a 70 kg patient is approximately \$1,176.

when the calcium of the medium is not supplemented and 0.5 mg/L when the calcium concentration is 50 mg/L. A reduction of the MIC₉₀ is seen with culture medium calcium supplementation in all other gram-positive isolates evaluated. They proposed a breakpoint for daptomycin in a culture medium with calcium supplementation of 50 mg/L to be 2 mg/L. All *Staphylococcus* isolates were inhibited similarly by daptomycin and quinupristin-dalfopristin, but less so by linezolid. The activity against

TABLE 1. SUSCEPTIBILITY OF GRAM-POSITIVE ISOLATES TO DAPTOMYCIN

Isolate	N	MIC ₅₀ Range (mcg/mL)	MIC ₅₀ (mcg/mL)	MIC ₉₀ (mcg/mL)	Reference
MSSA	50	0.12-0.5	0.5	0.5	4
MSSA	27	0.06-1	0.25	1	7
OSSA	888	≤0.015-1	ND	0.5	5
OSSA	713	0.03-0.5	ND	0.25	6
MRSA	54	0.5-1	1	1	7
MRSA	50	0.25-0.5	0.25	0.5	4
MRSS	29	0.25-1	0.5	1	7
ORSA	334	0.12-1	ND	0.5	5
ORSA	305	0.12-0.5	ND	0.5	6
<i>S. epidermidis</i>	20	0.12-.05	0.5	0.5	4
<i>S. saprophyticus</i>	30	0.25-1	0.5	0.5	4
CNS	1126	≤0.015-2	ND	0.5	6
OSCNS	486	0.03-1	ND	0.5	5
ORCNS	554	0.03-1	ND	0.5	5
<i>S. pneumoniae</i>	99	0.012-0.5	0.25	0.25	4
PSSP	619	≤0.015-1	ND	0.25	5
PSSP	728	≤0.015-0.25	ND	0.12	6
PSSP	16	0.015-0.5	0.03	0.125	7
PISP	165	0.03-0.5	ND	0.25	5
PISP	248	≤0.015-0.5	ND	0.25	6
PISP	21	0.008-1	0.25	1	7
PRSP	81	0.06-1	ND	0.25	5
PRSP	187	≤0.015-0.25	ND	0.12	6
PRSP	24	0.015-1	0.5	1	7
<i>S. pyogenes</i>	484	≤0.015-0.5	ND	0.06	6
<i>S. pyogenes</i>	10	0.008-0.5	0.015	0.125	7
<i>S. milleri</i>	30	0.25-1	0.5	1	4
Viridans streptococci	369	≤0.015-2	ND	1	6
<i>S. agalactiae</i>	367	0.06-1	ND	0.25	5
<i>S. agalactiae</i>	273	0.03-0.5	ND	0.25	6
<i>E. faecium</i>	333	0.03-8	ND	4	5
<i>E. faecium</i>	147	0.06-8	ND	4	6
<i>E. faecium</i>	25	1-4	2	2	4
<i>E. faecium</i> -VR	114	0.25-4	ND	2	5
<i>E. faecium</i> -VR	219	0.25-4	ND	4	6
<i>E. faecalis</i>	1798	≤0.015-4	ND	2	5
<i>E. faecalis</i>	2049	0.03-4	ND	2	6
<i>E. faecalis</i>	20	0.25-2	1	1	7
<i>E. faecalis</i>	24	0.5-4	1	2	4
<i>E. faecalis</i> -VR	40	0.05-4	ND	2	5
<i>E. faecalis</i> -VR	40	≤0.015-2	ND	2	6
<i>E. faecalis</i> -VR	23	0.5-2	1	2	7
<i>Enterococcus</i> spp.	160	≤0.015-4	ND	4	5
<i>Enterococcus</i> spp.	80	0.03-8	ND	4	6

MSSA - Methicillin-susceptible *Staphylococcus aureus*
 MRSA - Methicillin-resistant *Staphylococcus aureus*
 MRSS – methicillin-resistant *Staphylococcus* spp.
 CNS - Coagulase-negative *Staphylococcus* species
 ND - Not determined
 OSSA - Oxacillin-susceptible *Staphylococcus aureus*
 ORSA - Oxacillin-resistant *Staphylococcus aureus*

OSCNS - Oxacillin-susceptible coagulase-negative *Staphylococcus* spp.
 ORCNS - Oxacillin-resistant coagulase-negative *Staphylococcus* spp.
 PSSP - Penicillin-susceptible *Streptococcus pneumoniae*
 PISP - Penicillin-intermediate *Streptococcus pneumoniae*
 PRSP - Penicillin-resistant *Streptococcus pneumoniae*
 VR - Vancomycin-resistant enterococci

Enterococcus faecalis and *Enterococcus faecium* were comparable between daptomycin and linezolid. This includes the four *Enterococcus faecalis* strains that were resistant to vancomycin.

Critchley and colleagues studied the activity of daptomycin on bacterial isolates obtained from 40 sites in 15 European countries, and found it to be as active as quinupristin-dalfopristin (MIC₉₀ 0.5 mg/L) and linezolid (MIC₉₀ 2 mg/L) against oxacillin-resistant *Staphylococcus aureus*.⁵ With oxacillin-resistant coagulase-negative *Staphylococcus*, the MIC₉₀ of quinupristin-dalfopristin, daptomycin and linezolid were 0.25, 0.5, and 2 mg/L, respectively. Compared to quinupristin-dalfopristin and linezolid, daptomycin was more active against penicillin-resistant *Streptococcus pneumoniae*. Against *Streptococcus agalactiae*, daptomycin was equivalent to quinupristin-dalfopristin and more active than linezolid, but less active than the beta-lactam agents.

A second study by Critchley and colleagues examined gram-positive bacteria isolated in the United States.⁶ Daptomycin was active *in vitro* against oxacillin-resistant *Staphylococcus aureus* with an MIC₉₀ of 0.5 mg/L compared to linezolid with an MIC₉₀ of 4 mg/L. Against coagulase-negative *Staphylococcus*, daptomycin was also more active than linezolid. Against *Streptococcus* isolates, daptomycin was as active as vancomycin, linezolid and quinupristin-dalfopristin. When evaluating *Enterococcus faecalis*, daptomycin was as active as linezolid against vancomycin-resistant isolates, but linezolid was more active than daptomycin when testing other *Enterococcus* species.

Snydman and associates looked at 224 isolates and showed daptomycin to be more active *in vitro* than vancomycin to *Staphylococcus* isolates (methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus* species, and methicillin-susceptible *Staphylococcus aureus*), *Streptococcus pyogenes* and *Enterococcus faecalis*.⁷ Daptomycin was bactericidal in 82% of the vancomycin-resistant *Enterococcus faecium* isolates.

Gram-positive anaerobes

Goldstein and partners evaluated the antimicrobial activity against 338 corynebacteria and gram-positive anaerobic isolates (see Table 2).⁸ Daptomycin was compared to linezolid, quinupristin-dalfopristin and imipenem against 18 strains of *Clostridium difficile*. Daptomycin was active against all 18 strains, whereas linezolid, quinupristin-dalfopristin and imipenem each had diminished activity against three strains. There were 19 strains of *Clostridium innocuum* for which vancomycin was considerably less active than daptomycin. Although daptomycin was not active against five strains of *Lactobacillus* species, there were 16 strains that were vancomycin-resistant that were susceptible to daptomycin. In the *Actinomyces* species, vancomycin was more active than daptomycin.

In vitro, Silverman and affiliates showed the resistance of bacteria to daptomycin is dependent on the calcium concentration as well as to culture density.⁹ Eight clinical and eight laboratory isolates (four strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis* and two strains of *Enterococcus faecium* and *Streptococcus pneumoniae*) were evaluated on a culture medium supplemented with 1 mM calcium chloride. No resistant organisms were noted.

There has been no cross-resistance noted between daptomy-

cin and vancomycin or any other antibiotic.¹ In phase II and III clinical trials, daptomycin resistance occurred in less than 0.2% of over 1,000 subjects. One case of resistance was observed in a patient with *Staphylococcus aureus* who received daptomycin in a dose lower than protocol-specified for the initial five days. The second occurrence of resistance in a patient with *Enterococcus faecalis* who was enrolled in a salvage trial.¹

CLINICAL TRIALS

At the time of this writing, no *in vivo* clinical trials have been published in any peer-reviewed journal. However, data from abstracts are available regarding the clinical efficacy of daptomycin. Companaro and colleagues completed two multi-national, investigator-blinded, randomized studies evaluating the noninferiority of daptomycin against comparator agents.¹⁰ In these studies, 1,092 patients ages 18 to 85 with complicated skin and skin structure infections were randomized to receive either daptomycin 4 mg/kg once daily or a comparator, and were treated for seven to 14 days. The comparator was either vancomycin 1 g every 12 hours or a penicillinase-resistant penicillin (PRP) 4-12 g/day. Before each patient was randomized, the primary investigator evaluated the patient and chose which comparator (vancomycin or PRP) the patient would receive if randomized to the comparator group. The penicillinase-resistant penicillins utilized were oxacillin, nafcillin, cloxacillin and flucloxacillin. The PRP chosen depended on the availability of the PRP at the particular treatment center. All patients were then evaluated at baseline and for six to 20 days post-treatment for clinical and microbiologic outcomes.

Clinical success was defined as resolution of signs and symptoms and the determination that no additional antibiotic therapy was needed. Clinical success was obtained in 71.5% of the daptomycin group and 71.1% of the comparator group (95% CI, -5.8 to 5.0). Data analysis from 902 subjects defined as clinically evaluable was also completed. A patient was defined as clinically evaluable if all major protocol criteria such as duration of therapy, inclusion and exclusion criteria and evaluations were met. In the daptomycin group the clinical success was 81.1% compared to vancomycin 73.5% (95% CI, -17.4 to 2.9). In the daptomycin group that was compared to PRPs, the clinical success was 87.3% whereas the PRP clinical success was 90.5% (95% CI, -1.9 to 8.3).

Patients who achieved clinical success were then evaluated for new infections and clinical relapse at a post-study evaluation, 20-28 days after the completion of therapy. Relapse or new clinical infection occurred in 4.2% (15 of 355) of the daptomycin patients and 5.5% (20 of 367) of the patients receiving a comparator (95% CI, -4.4 to 1.9).

ADVERSE EFFECTS

In phase III clinical trials, 2.7% of patients discontinued daptomycin due to adverse events, while the comparator medication was discontinued in 2.8% of patients.^{1,10} Adverse events reported were constipation (6.2%), nausea (5.8%), diarrhea (5.2%), vomiting (3.2%), injection site reactions (5.8%), fever (1.9%), headache (5.4%), insomnia (4.5%), dizziness (2.2%), rash

TABLE 2. ACTIVITY OF DAPTOMYCIN AGAINST GRAM-POSITIVE ANAEROBES AND CORYNEBACTERIUM

Isolate	n	MIC Range (mcg/mL)	MIC ₅₀ (mcg/mL)	MIC ₉₀ (mcg/mL)	Reference
<i>Actinomyces</i> spp.	22	0.06-16	2	4	8
<i>Bifidobacterium</i> spp.	13	≤0.03-1	0.25	0.5	8
<i>Clostridium bifermentans</i> - <i>Clostridium sordellii</i> group	10	0.5-8	2	4	8
<i>Clostridium cadaveris</i>	10	0.5-8	2	4	8
<i>Clostridium clostridioforme</i>	10	0.5-8	2	4	8
<i>Clostridium difficile</i>	18	0.125-1	0.5	1	8
<i>Clostridium innocuum</i>	19	1-4	2	4	8
<i>Clostridium paraputrificum</i> - <i>Clostridium tertium</i> group	10	2-32	8	32	8
<i>Clostridium perfringens</i>	11	2-32	8	32	8
<i>Clostridium ramosum</i>	15	1-16	16	16	8
<i>Clostridium</i> spp.	25	≤0.03-2	0.5	2	8
<i>Eubacterium lentum</i>	17	0.125-16	2	16	8
<i>Eubacterium</i> group spp.	31	≤0.03-16	0.25	4	8
<i>Lactobacillus</i> spp.	37	≤0.03-32	1	16	8
<i>Peptostreptococcus asaccharolyticus</i>	10	≤0.03-125	≤0.03	0.06	8
<i>Peptostreptococcus magnus</i> - <i>Peptostreptococcus micros</i> group	14	0.125-1	0.5	1	8
<i>Peptostreptococcus</i> spp.	13	≤0.03-16	0.25	2	8
<i>Propionibacterium</i> spp.	15	0.125-2	0.5	2	8
<i>Corynebacterium jeikeium</i>	10	0.125-0.5	0.25	0.25	8
<i>Corynebacterium</i> spp.	21	≤0.03-8	≤0.03	1	8

ND - Not determined

*NCCL breakpoints are unavailable to interpret as susceptible, intermediate or resistant

(4.3%), pruritus (2.8%), fungal infections (2.6%), urinary tract infections (2.4%), hypertension (1.1%), renal failure (2.2%), anemia (2.1%), dyspnea (2.1%), limb pain (1.5%) and arthralgia (0.9%).

Observed changes in laboratory values include elevated creatine phosphokinase (CPK) that occurred in 2.8% of the patients receiving daptomycin and abnormal liver function tests that occurred in 3% of the patients.

Since an increase in creatine phosphokinase levels was reported in patients during clinical trials, the FDA has stated that CPK levels should be monitored weekly in patients on daptomycin. Patients should be monitored more frequently if an unexplained increase in CPK occurs.¹¹

COST, DOSE AND HOW SUPPLIED

The recommended dose of daptomycin is 4 mg/kg intravenously once daily, infused over 30 minutes. The dose should be reduced to 4 mg/kg once every 48 hours in patients whose creatinine clearance is less than 30 mL/min. The reconstituted drug should not be mixed or infused simultaneously with other drugs and diluents containing dextrose should not be used. Once reconstituted, daptomycin is stable, either in the vial or further diluted in an infusion bag, for a total of 12 hours at room temperature or 48 hours refrigerated. Daptomycin is supplied in vials of lyophilized powder containing 500 mg per vial.¹ The AWP for one vial is \$168. A seven-day course of therapy for a 70 kg patient would cost approximately \$1,176. This cost is similar to that of a seven-day course of linezolid (AWP \$1,196 for linezolid 600 mg every 12 hours), but is significantly more expensive than nafcillin (\$638 for 2 g every four hours) and vancomycin (\$85 for 1 g every 12 hours).

CONCLUSIONS

Daptomycin offers the convenience of once daily dosing with a drug that is active against gram-positive cocci and some anaerobes. An evaluation of abstracts from unpublished phase III clinical trials suggests that daptomycin achieves a clinical success rate similar to vancomycin and penicillinase-resistant penicillin when utilized for gram-positive organisms. Publication and critical review of these should occur before this product is considered for formulary addition. In the face of emerging multi-antibiotic resistant bacteria, daptomycin provides a unique mechanism of action. To prevent the development of bacterial resistance to daptomycin, if added to formulary, its use should be tightly restricted to instances where all other treatment options have failed. ●

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