

A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure infections

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Abstract: Daptomycin is a novel bactericidal antibiotic with excellent activity against gram-positive organisms. It is a large cyclic lipopeptide with a unique mechanism of action. Daptomycin is given once a day and is renally cleared, requiring dose adjustment in patients with impaired renal function. Unfortunately, there have been case reports of resistant gram-positive organisms. Daptomycin is generally well tolerated, though myopathy has been reported. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors should be stopped in patients on daptomycin. Daptomycin shows promise in experimental models of endocarditis, meningitis, ventriculitis, and peritonitis, and is currently approved for use in skin and soft-tissue infections. Daptomycin is a welcome newcomer to the gram-positive antimicrobial arsenal.

Keywords: daptomycin, lipopeptide, antibiotic, skin infection

Introduction

With the increasing numbers and types of resistant organisms, there is an increasing need for antibiotics to treat infections caused by them. Daptomycin is a cyclic lipopeptide with a broad spectrum of activity against gram-positive organisms, both aerobic and anaerobic. This includes resistant strains as well such as methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *Staphylococcus aureus* (GISA), vancomycin-resistant enterococci (VRE), coagulase-negative staphylococci (CoNS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP).

Daptomycin was discovered in the early 1980s, at Eli Lilly and Company (Tally and DeBruin 2000). Daptomycin was initially developed in the late 1980s and early 1990s but was ultimately shelved due to concerns regarding adverse effects, in particular drug-induced myopathy. Cubist Pharmaceuticals Inc. licensed worldwide rights from Eli Lilly and Company in 1997 (Tally and DeBruin 2000).

Basics/mechanism of action

Daptomycin is derived as a fermentation product from *Streptomyces roseosporus*. The unique structure of daptomycin consists of a 13-member amino acid cyclic lipopeptide with a decanoyl side-chain (Steenbergen et al 2005) (Figure 1). Daptomycin molecular weight is 1620.67 (Cubicin package insert 2003). This is a rather large molecule which may influence its distribution into tissues.

The exact details of daptomycin's mechanism of action are not completely understood. It is believed to have a unique mechanism of action that involves calcium-dependent insertion of the lipophilic daptomycin tail into the bacterial cell membrane,

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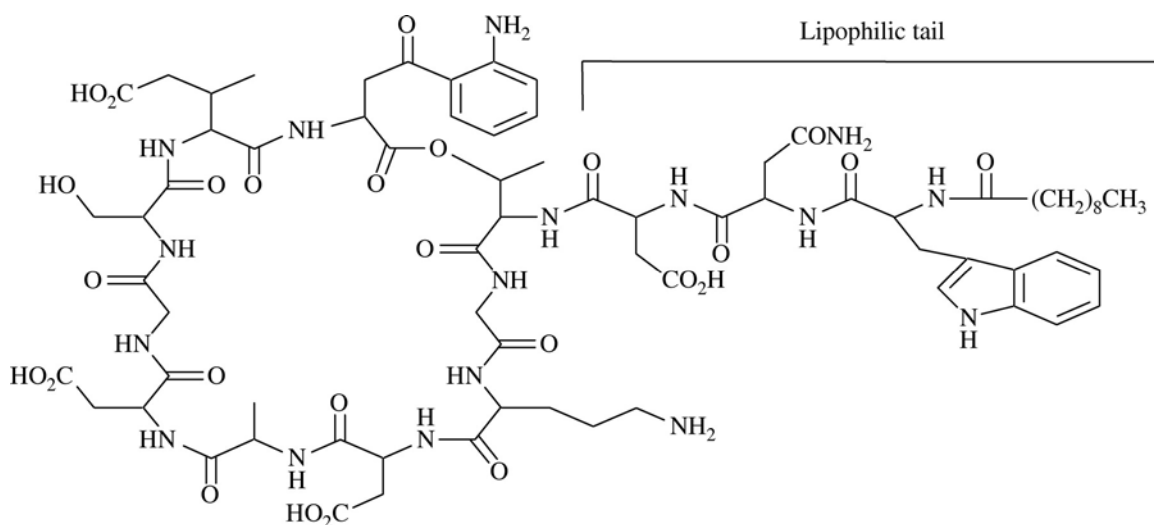


Figure 1 Structure of daptomycin. Copyright © 2005. Reproduced with permission from Steenbergen JN, Alder J, Thorne GM, et al. 2005. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother*, 55:283–8.

causing rapid depolarization and potassium ion efflux (Steenbergen et al 2005) (Figure 2). It has been observed that daptomycin causes a calcium-dependent dissipation of the membrane potential ($\Delta\psi$) in *Staphylococcus aureus* without noticeably affecting the chemical gradient (ΔpH) across the membrane (Alborn et al 1991). This unique mechanism of action makes daptomycin rapidly bactericidal.

Pharmacokinetics

Daptomycin exhibits linear pharmacokinetics across a wide range of doses with once daily dosing up to 6 mg/kg (Figure 3) (Woodworth et al 1992; Dvorchik et al 2003). Daptomycin doses of 8 mg/kg exhibit a slight nonlinearity (Dvorchik et al 2003).

Approximately 92% of daptomycin is protein-bound (Woodworth et al 1992). Excretion of the drug occurs primarily via the kidney with approximately 80% of the total dose, of which two-thirds is intact drug, recovered in the urine (Tally and DeBruin 2000). Due to daptomycin's predominant renal clearance, it requires dose adjustments in those with impaired renal function. Daptomycin clearance in females is estimated to be approximately 80% that of males with similar renal function, although this has otherwise not been shown to be statistically or clinically significant (Dvorchik et al 2004).

The observed $t_{1/2}$ is relatively long (~9 hours) (Dvorchik et al 2003). The long $t_{1/2}$ allows for once daily dosing in patients with normal renal function. Daptomycin $t_{1/2}$ is increased by 2.3-fold in patients with creatinine clearance (CL_{cr}) <40 mL/min and 3.5-fold in patients on dialysis (Dvorchik et al 2004).

Daptomycin remains in the plasma and interstitial fluid and therefore has a small volume of distribution (Dvorchik et al 2003, 2004).

The maximum serum concentration after escalating single daily doses of daptomycin ranged from approximately 55, 85 to 95 $\mu\text{g/mL}$, and 115 to 130 $\mu\text{g/mL}$ with doses of 4, 6, and 8 mg/kg, respectively (Dvorchik et al 2003). The area under the curve following doses of 4, 6, and 8 mg/kg/day revealed similar linearity to the C_{max} pharmacokinetic data above (Dvorchik et al 2003, 2004).

Daptomycin has been shown to exhibit a post-antibiotic effect (PAE) on *Staphylococcus aureus* and *Streptococcus pneumoniae* (Pankuck et al 2003; Safdar et al 2004). The PAE combined with the long $t_{1/2}$ of daptomycin allows for once daily dosing in patients with normal renal function.

Daptomycin should not be used to treat pneumonia. This is due to the fact that daptomycin is inhibited by surfactant (Silverman et al 2005).

Spectrum of activity

As mentioned before, daptomycin has a broad spectrum of activity against gram-positive organisms, both aerobic and anaerobic. This includes resistant strains as well such as MRSA, GISA, VRE, CoNS, and PRSP. Calcium concentration of the media is an important factor in interpreting susceptibility testing (Fuchs et al 2000). The manufacturer recommends susceptibility testing with broth microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L (Cubicin package insert 2003). Below are the minimum inhibitory concentration of anti-infective needed to inhibit the growth of 90% of strains

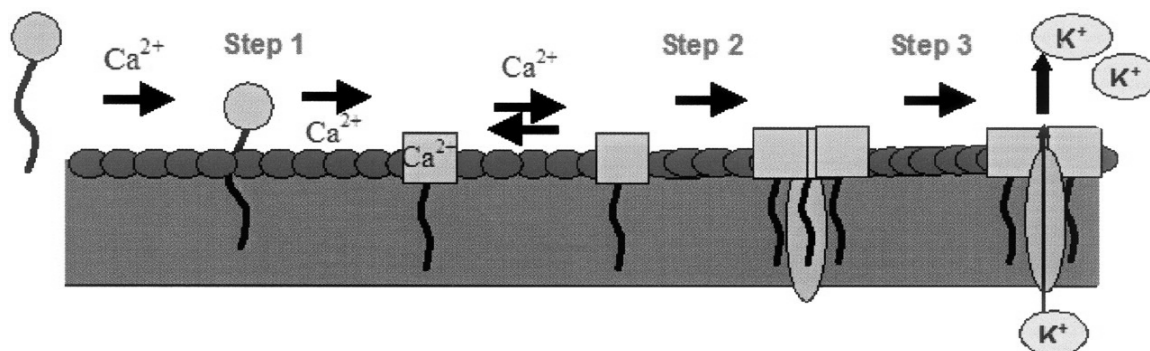


Figure 2 Proposed mechanism of action of daptomycin. Hypothetical steps: step 1, daptomycin binds to the cytoplasmic membrane in a calcium-dependent manner; step 2, daptomycin oligomerizes, disrupting the membrane; step 3, the release of intracellular ions and rapid cell death. Copyright © 2005. Reproduced with permission from Steenbergen JN, Alder J, Thorne GM, et al. 2005. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother*, 55:283–8.

(MIC₉₀s) of a variety of gram-positive organisms from various in vitro studies:

- *Staphylococcus aureus** MIC 0.5 mg/L (Streit et al 2004) (*without a breakdown into MSSA and MRSA).
- MSSA MIC 0.25 to 0.5 mg/L (Wise et al 2001; Fuchs et al 2002; Richter et al 2003).
- MRSA MIC 0.5 to 1.0 mg/L (Wise et al 2001; Fuchs et al 2002; Richter et al 2003).
- GISA MIC 0.125–0.5 mg/L (Akins and Rybak 2000, 2001). No differences were seen for susceptibility of *vanA*, *vanB1*, and *vanD* strains (Jevitt et al 2003).
- VRSA: Daptomycin was found to be bactericidal against a VRSA (strain HMC3) isolated in Pennsylvania, US that was resistant to vancomycin through the presence of the *vanA* resistance gene; it also contained *mecA*, *erm(A)*, *erm(B)*, *tet(K)* and *aac(6′)-aph(2′′)*, conferring resistance to licensed β-lactams, macrolides, tetracycline and aminoglycosides (Bozdogan et al 2003).
- CoNS 0.5 mg/L (Wise et al 2001; Fuchs et al 2002; Sader et al 2004; Streit et al 2004).
- *Enterococcus faecalis*** MIC 1 to 2 mg/L (Wise et al 2001; Richter et al 2003; Streit et al 2004) (**Enterococci were defined as vancomycin susceptible and those not further defined. If known to be VRE then stated as such).
- Vancomycin-resistant *Enterococcus faecalis* MIC 1 to 4 mg/L (Richter et al 2003; Sader et al 2004).
- *Enterococcus faecium* MIC 2 to 4 mg/L (Wise et al 2001; Richter et al 2003; Streit et al 2004).
- Vancomycin-resistant *Enterococcus faecium* MIC 2 to 4 mg/L (Richter et al 2003; Sader et al 2004).
- *Streptococcus pneumoniae* MIC 0.25 mg/L (Wise et al 2001; Streit et al 2004).
- PRSP MIC 0.25 mg/L (Sader et al 2004).

Susceptibility breakpoints for as set forth by the Food and Drug Administration (FDA), which are the same as those from the National Committee for Clinical Laboratory Standards, are as follows (Cubicin package insert 2003; Streit et al 2005):

- *Staphylococcus aureus* (MSSA and MRSA) <1 mg/L
- *Streptococcus spp.* (*S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* subsp. *equisimilis*) ≤1 mg/L
- *Enterococcus faecalis* (vancomycin-susceptible only) <4 mg/L

Resistance

There appears to be a low rate of spontaneous resistance to daptomycin with limited increases in MIC and relative ease of treatment of resistant isolates (Silverman et al 2001).

Population analysis of three *Staphylococcus aureus* isolates for which the daptomycin MICs were 8 mg/mL showed a pattern of homogeneous resistance (Jevitt et al 2003).

There have been multiple case reports of gram-positive organisms with daptomycin resistance, these include MRSA (Mangili et al 2005), *Enterococcus faecium* (Sabol et al 2005; Long et al 2005), and *Enterococcus faecalis* (Munoz-Price et al 2005).

Adverse drug reactions

Early in clinical trials daptomycin was found to have skeletal muscle effects that included myopathy with muscle weakness and elevated serum creatine phosphokinase (CPK). Further testing using a dog model revealed that this was more of a problem with fractionated dosing that could be overcome by changing the dosing schedule to once daily from every twelve hours (Oleson et al 2000).

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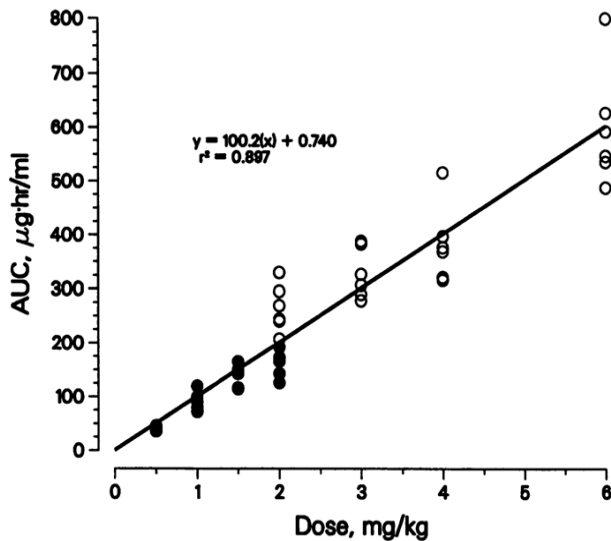


FIG. 3. Linearity of dose versus AUC between 0.5 and 6 mg/kg. ●, AUCs from study B; ○, AUCs from study C.

Figure 3 Linearity of dose versus area under the curve (AUC). Copyright © 1992. Reproduced with permission from Woodworth JR, Nyhart EH, Brier GL, et al. 1992. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob Agents Chemother*, 36:318–25.

Daptomycin is generally well tolerated (Dvorchik et al 2003; Arbeit et al 2004). A large randomized trial evaluating the safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections (cSSSI) involving 1092 patients revealed the frequency, distribution, and severity of adverse events to be similar for daptomycin and standard therapy (Arbeit et al 2004) (Table 1).

There was a case report of significant myopathy with daptomycin without pronounced CPK elevation (CPK <500 U/L) at a dose of 6 mg/kg intravenously per day (Veligandla et al 2004). There has also been a case report of myopathy and possible hepatotoxicity in a patient with underlying chronic liver disease, but the elevations in the transaminases were mild (aspartate aminotransferase 239 U/L and alanine aminotransferase 48 U/L) (Echevarria et al 2005). It is recommended by the manufacturer that in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000 U/L, or in patients without reported symptoms who have marked elevation in CPK ($\geq 10 \times$ ULN), daptomycin should be discontinued (Cubicin package insert 2003).

Drug–drug interactions

Daptomycin is without any known significant drug–drug interactions. Nonetheless, the manufacturer recommends

giving consideration to temporarily discontinuing use of HMG CoA reductase inhibitors while patients receive daptomycin (Cubicin package insert 2003). This is recommended due to the potential confusion that may arise if a patient on an HMG CoA reductase inhibitor were to experience myopathy or an increase in CPK level.

Clinical uses

Daptomycin is currently only approved for the treatment of cSSSI caused by susceptible *Staphylococcus aureus* (MSSA and MRSA), *Streptococcus spp.* (*S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* subsp. *equisimilis*), and *Enterococcus faecalis* (vancomycin-susceptible only) (Cubicin package insert 2003; Arbeit et al 2004). This includes diabetic foot ulcers (Arbeit et al 2004; Lipsky and Stoutenburgh 2005).

Daptomycin has proven to be effect in multiple experimental endocarditis models. In a retrospective analysis of 49 patients with endocarditis due to gram-positive organisms, daptomycin dosed at >6 mg/kg intravenously every 24 hours showed high cure rates (Levine and Lamp 2005).

There have also been case reports of successful treatment of prosthetic valve endocarditis in humans (Mohan et al 2005). Daptomycin trials in human endocarditis are currently in progress.

In an experimental animal (rabbit) model of meningitis due to penicillin- and quinolone-resistant *Streptococcus pneumoniae*, daptomycin looked promising when compared with the combination of ceftriaxone and vancomycin (Cottagnoud et al 2004).

In an experimental model of *Staphylococcus aureus* ventriculitis in hydrocephalic rabbits, daptomycin was detectable in the periventricular white matter but in amounts too small to quantitate. Daptomycin killed more *Staphylococcus aureus* more rapidly than vancomycin in this model (Haworth et al 1990).

Daptomycin also appears to be a promising for the treatment of peritoneal dialysis-associated peritonitis due to staphylococci and streptococci in an in vitro peritoneal dialysate model (Hermsen et al 2003).

A trend toward equivalent efficacy between intravenous daptomycin and intravenous ciprofloxacin was observed in the treatment of gram-positive urinary tract infections in which *Enterococcus faecalis* and *Staphylococcus aureus* were the most common gram-positive pathogens (Naber et al 2004). Based on the previously mentioned susceptibilities and the fact that daptomycin is predominately renally excreted, one would predict that daptomycin should be

Table 1 Adverse events that occurred in >2% of patients in either treatment group (Arbeit et al 2004)

Adverse event	n (%) of patients	
	Daptomycin group (n=534)	Comparator group ^a (n=558)
Constipation	33 (6.2)	38 (6.8)
Nausea	31 (5.8)	53 (9.5)
Injection site reaction	31 (5.8)	43 (7.7)
Headache	29 (5.4)	30 (5.4)
Diarrhea	28 (5.2)	24 (4.3)
Insomnia	24 (4.5)	30 (5.4)
Rash	23 (4.3)	21 (3.8)
Vomiting	17 (3.2)	21 (3.8)
Abnormal liver function test results	16 (3.0)	9 (1.6)
Pruritus	15 (2.8)	21 (3.8)
Elevated serum CPK level	15 (2.8)	10 (1.8)
Fungal infection	14 (2.6)	18 (3.2)
Hypotension	13 (2.4)	8 (1.4)
Urinary tract infection	13 (2.4)	3 (0.5)
Renal failure	12 (2.2)	15 (2.7)
Dizziness	12 (2.2)	11 (2.0)
Anemia	11 (2.1)	13 (2.3)
Dyspnea	11 (2.1)	9 (1.6)
Fever	10 (1.9)	14 (2.5)
Limb pain	8 (1.5)	11 (2.0)
Hypertension	6 (1.1)	11 (2.0)
Dyspepsia	5 (0.9)	14 (2.5)
Arthralgia	5 (0.9)	12 (2.2)

Note: ^aCloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

Abbreviations: CPK, creatine phosphokinase.

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effective in the treatment of urinary tract infections due to such pathogens, but this warrants further studies.

Daptomycin was at least equivalent to vancomycin against chronic foreign body infections due to *Staphylococcus aureus*, though vancomycin has poor activity in these infections. In a prospective study of daptomycin in the treatment of prosthetic joint infections, 5 of 7 patients with MRSA infections experienced treatment failures, so the efficacy of daptomycin in the treatment of prosthetic joint infections is uncertain (Rao and David 2005).

Daptomycin should not be used to treat pneumonia. This is due to the fact that daptomycin is inhibited by surfactant (Silverman et al 2005).

Dose

The dose of daptomycin is 4 mg/kg intravenously every 24 hours for patients with normal renal function (Cubicin package insert 2003; Arbeit et al 2004). For patients with a

creatinine clearance of less than 30 mg/min, including those patients on hemodialysis, continuous ambulatory peritoneal dialysis, or continuous renal replacement therapy (CRRT) which includes continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemofiltration (CVVH), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF), the dose is 4 mg/kg intravenously every 48 hours (Cubicin package insert 2003; Arbeit et al 2004; Trotman et al 2005). Patients with moderate hepatic impairment receiving daptomycin do not require an adjustment in daptomycin dose or dose regimen (Dvorchik 2004). No adjustment in daptomycin dose or dose regimen should be required based solely on obesity (Dvorchik and Damphousse 2005). An international, multicenter, randomized open label trial using the off-label dose of daptomycin at 6 mg/kg every 24 hours showed that this dose was similar in efficacy to standard therapy for *Staphylococcus aureus* bacteremia and endocarditis (Fowler et al 2005).

Conclusion

Daptomycin is a cyclic lipopeptide antibiotic with excellent activity against gram-positive organisms. Although there have been case reports of daptomycin-resistant gram-positive organisms, it has a unique mechanism of action that renders it bactericidal. Daptomycin is given once a day and is renally cleared, requiring dose adjustment in patients with impaired renal function. Daptomycin is generally well tolerated, though myopathy has been reported. Daptomycin is currently approved for use in skin and soft-tissue infections and shows promise in experimental models of endocarditis, meningitis, ventriculitis, and peritonitis.

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