

Daptomycin: Beyond FDA-Approved Indications

by Sara Randolph, Pharm.D.

In a world wrought with multi-drug resistant organisms, the need to fight superbugs with superdrugs becomes essential. Daptomycin (Cubicin[®]), with its novel mechanism of action, is FDA approved for the treatment of complicated skin and soft tissue infections; however, it has also been used to treat vancomycin-resistant enterococcus (VRE) and bacteremia.^{1,2} Since addition to the UW Medicine Drug Formulary in the fall of 2004, the use of daptomycin for the treatment of resistant pathogens has continued to evolve. This article will briefly review the pharmacology of daptomycin and summarize the literature supporting its use for non-FDA-approved indications.

Daptomycin is the first drug in a new class of antibiotics known as lipopeptides, derived from the fermentation of *Streptomyces roseosporus*. Daptomycin has shown activity against *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *S. agalactiae*, group C and G β -hemolytic strep and vancomycin-susceptible and resistant VRE.⁵ Unlike linezolid and quinupristin-dalfopristin, daptomycin is bactericidal against enterococcus and many other gram-positive pathogens. Daptomycin rapidly depolarizes cells by binding to bacterial membranes and causing potassium efflux. This loss of cell membrane potential leads to inhibition of protein, DNA, and RNA synthesis, culminating in bacterial cell death. This mechanism is unique because it occurs without lysis, is concentration dependent, and is very rapid.⁴

The relevant pharmacokinetic parameters of daptomycin are summarized in Table I. Daptomycin displays linear kinetics at typical doses of 4mg/kg but exhibits nonlinear kinetics as doses approach 8mg/kg.⁵ The half-life of daptomycin is between 8 and 9 hours, but can be prolonged in patients with renal dysfunction. Daptomycin is ~90–95% reversibly bound to human plasma proteins in a concentration-independent manner. Excretion of daptomycin is primarily via the kidneys, therefore dosage adjustments are necessary in patients with creatinine clearance (Crcl) <30mL/minute. Recommended dosing of daptomycin for the FDA-approved indication of complicated skin and soft tissue infections is 4mg/kg every 24 hours. For patients with Crcl <30mL/minute, the manufacturer recommends 4mg/kg every 48 hours. If patients are being hemodialyzed, it will be necessary to dose daptomycin after dialysis, as 15% of the drug is removed. Cubist Pharmaceuticals conducted an open-label, single-dose, parallel-group study of daptomycin kinetics in 24 healthy, adult volunteers given 4mg/kg based on total body weight.⁶ Moderately obese (BMI 25–39.9kg/m²) or morbidly obese (\geq 40kg/m²) subjects were matched to non-obese controls. The volume of distribution and clearance were increased in the obese subjects compared to the controls. The AUC and C_{max} were increased significantly, but no untoward effects related to daptomycin were observed. The conclusion of the study was that daptomycin should be dosed based on TBW; however, safety data in seriously ill obese patients is not yet available and prescribers should consider dosing based on adjusted body weight in such patients.

(Continued on page 30)

A University of Washington Drug Information Center publication
Distributed monthly by authority of the Pharmacy and Therapeutics Committee
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
Department of Pharmacy Services / School of Pharmacy

Copyright © 2005 by the University of Washington
Also published on the World Wide Web at <http://uw.prnrx.org/therapyTopics.asp>
No material may be reproduced in whole or in part without written permission from the editor.

AUC _{24h}	494 mcg x h/mL
C _{max}	57.8 mcg/mL
Protein binding	90-95%
V _d	0.1 L/kg
Elimination	Renal
T _{1/2}	7.5-8 hours

Daptomycin has a unique bacteriocidal mechanism of action: It causes rapid potassium efflux and cellular depolarization followed by cell death.

Daptomycin has obtained FDA approval for the treatment of complicated skin and soft tissue infections. However, as there are more effective and cheaper alternatives for these infections, daptomycin should be reserved for infections caused by multi-drug resistant pathogens.

An ongoing clinical trial will clarify the role of daptomycin for the treatment of infective endocarditis.

To date, several investigators have attempted to determine the MICs of daptomycin. Johnson and colleagues looked at the activity of daptomycin against 545 multi-drug resistant isolates.¹ The panel was comprised of enterococci (including *E. faecalis* and *E. faecium*), MRSA, streptococci, and corynebacterium species. Interestingly, daptomycin's minimum inhibitory concentration was slightly higher for both enterococcus species (<2–4 mg/L). The MICs for almost all other organisms were found to be <1mg/L. The authors concluded that *in vitro* activity of daptomycin showed promise against gram-positive bugs. The most important fact Johnson and colleagues uncovered is that daptomycin was active against strains of organisms resistant to linezolid and quinupristin/dalfopristin (see Table II).

Daptomycin is not a new kid on the block. Eli Lilly discovered daptomycin in the early 1980s, but shelved the product, possibly because in the pre-VRE era, the risk-to-benefit ratio was not perceived to be favorable due to cases of skeletal muscle toxicity when dosed twice daily. Cubist Pharmaceuticals later purchased the rights to daptomycin and it was FDA approved in 2003. Because this drug has been around for many years, early safety trials date back to the 1980s. In trials using doses of 3–4mg/kg every 12 hours, profound myopathies were identified.² Two out of 5 patients were noted to have elevations in serum creatine phosphokinase that reached up to 10 times the upper limit of normal. These elevations were late in onset (occurring one week after treatment initiation) and were reversible after discontinuation of therapy. Subsequent studies in animals suggest that these toxicities are correlated with elevated trough concentrations.⁵ Because of this finding, doses of 4mg/kg every 24 hours rather than every 12 hours were used in subsequent trials.⁵ In these, the side-effect profile of daptomycin was not significantly different from the control group. Thus, daptomycin should be closely monitored in patients with renal dysfunction and in those who are on other medications known to be associated with myopathies (e.g., statins). Also, healthcare providers should discontinue the drug immediately if patients are noted to have elevated creatine phosphokinase >5 times the upper limit of normal.

Infectious disease practitioners are beginning to use daptomycin off-label for serious infections. One of these infections, endocarditis, is particularly challenging to cure due to the static environment of the fibrin clot (or vegetation) requiring prolonged antimicrobial therapy. In the age of VRE, and compounded by reports of documented linezolid-resistant enterococcus⁷ and glycopeptide intermediate-sensitive *S. aureus* (GISA), finding alternative bacteriocidal therapies is again crucial. Mohan, et al., published a recent case report of a patient with MRSA prosthetic aortic valve endocarditis

Table II: Overview of the *In Vitro* Activity of Selected Agents Against Specific Multi-resistant Pathogens (MIC₅₀, MIC₉₀, and Range values in mg/L)¹

Organism	Daptomycin			Linezolid			Quinupristin/dalfopristin			Vancomycin		
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range
<i>E. faecalis</i>	1	1	0.5-2	2	32	4-64	16	32	4-64	>128	>128	1->128
<i>E. faecium</i>	2	2	0.25-4	2	16	2-64	1	16	0.5-32	>128	>128	0.5->128
MRSA	0.5	1	0.25-1	2	2	1-16	0.5	1	0.25-1	1	2	1-4
MSSA	0.5	0.5	0.25-1	2	2	1-4	0.5	0.5	0.25-1	2	2	1-2
<i>Strep viridans</i>	0.5	1	0.06-1	1	2	0.5-2	–	–	–	0.5	1	0.5-1
<i>C. jeikeium</i>	0.5	1	0.125-1	1	1	0.5-1	–	–	–	1	1	0.5-2

Given the limited availability of data, use of daptomycin should only be considered in consultation with the ID service.

While daptomycin may turn out to be an attractive drug for endocarditis, it CANNOT be used for pneumonia.

Skeletal muscle toxicity from daptomycin increases at doses higher than the usual dose of 4mg/kg/day.

Table III: UW Acquisition Costs for Daptomycin and Other Formulary Options

Regimen	Cost for 10-days
Daptomycin 4mg/kg q 24h	\$1420
Linezolid 600mg q12h	\$1338
Quinupristin/dalfopristin 500mg q 8h	\$2993
Vancomycin 1g q 12h	\$109

While the mechanism is currently unknown, bacterial resistance to daptomycin is expected to increase over time.

References available upon request.

Note: The editor gratefully acknowledges the assistance of Jeannie Chan, Pharm.D. and Timothy Dellit, M.D., HMCAARM Team, and Doug Black, Pharm.D. in reviewing this article.

complicated by a valve abscess and bacteremia, which was resistant to linezolid and vancomycin.⁸ The patient refused further surgeries, thus the abscess could not be drained. Physicians decided to treat the patient with high doses of daptomycin (6mg/kg) every 24 hours. By day 5 cultures were negative and transesophageal echocardiogram showed a decrease in the abscess size after one week. Currently, an ongoing, multicenter, randomized open-label Phase 3 study is underway to determine if daptomycin 6mg/kg every 24 hours is effective for endocarditis.² Daptomycin is being compared to conventional therapy with nafcillin, oxacillin, or cloxacillin at doses of 2g every 4 hours for MSSA infections or with vancomycin 1g every 12 hours for MRSA infections. If left-sided endocarditis is diagnosed, gentamicin is added regardless of treatment arm. The length of therapy is set at 10–42 days, based on susceptibility data; however, at the discretion of the investigator, therapy may be prolonged. Patients are to be excluded if they have severe renal dysfunction characterized by a CrCl<30mL/minute, or if they have a prosthetic heart valve. The study is expected to conclude in the spring of 2005. Given the limited availability of data, the use of daptomycin in this setting should be accompanied by consultation with the infectious disease service.

While daptomycin may be beneficial in endocarditis, it cannot be used for pneumonia. In two phase II randomized, multicenter, double-blind trials comparing the efficacy and safety of daptomycin 4mg/kg q day versus ceftriaxone 2g q day, daptomycin failed to meet the predetermined criteria for noninferiority. Therefore, due to limited penetration and accumulation of daptomycin into lung tissue, it should not be used for any case of pneumonia, including MRSA pneumonia.⁹

Although daptomycin is more expensive than vancomycin and similar in price to parenteral linezolid (see Table III), it is cheaper than quinupristin/dalfopristin (Synercid[®]). Considering its fairly benign safety profile (when dosed q 24h) and unique bacteriocidal mechanism of action, daptomycin likely has a niche in fighting the war on multi-drug resistant organisms. However, available data do not support its role as a first-line agent at this time.

Growing antibiotic resistance continues to plague the globe. To date, initial daptomycin resistance has not been reported and the incidence of spontaneous resistance has been very low.¹⁰ The mechanism by which resistance to daptomycin develops is unknown. A case report published in April 2005 describes one of the first treatment failures associated with daptomycin.¹¹ The 54-year-old patient with end-stage liver disease and daptomycin-susceptible MRSA of the portal vein was treated initially with daptomycin. After 27 days of treatment, bacteremia continued and daptomycin resistance was detected. Treatment was changed to linezolid and negative cultures were obtained 5 days later. With more mainstream use, the incidence of daptomycin resistance is likely to increase over time.

Daptomycin is FDA approved for treatment of complicated skin and soft tissue infections caused by sensitive gram-positive organisms, MRSA, and vancomycin-susceptible *Enterococcus faecalis*; but not for VRE. Fortunately, there are almost always less expensive, and therefore more appropriate drugs, that are effective to treat non-life-threatening infections. Because of daptomycin's rapid, concentration-dependent bactericidal killing, this drug has theoretical advantages over drugs such as quinupristin-dalfopristin and linezolid. Daptomycin is associated with few side effects when dosed once daily. However, in this era of antibiotic resistance, it is essential that prescribers realize that daptomycin should be reserved for a very narrow niche of life-threatening, multi-drug resistant infections. This niche is likely to evolve with publication of the results of ongoing clinical trials.

Penicillin Allergy: Asking the Important Questions

by Donna Mabe, Pharm.D. (Extracted from *Drug Therapy Topics* 2002; 31(1):1-6.)

Due to fear of anaphylaxis, the use of β -lactams (penicillins, cephalosporins, carbapenems, and monobactams) is sometimes limited by a vague history of “penicillin allergy.” Coupled with an understanding of β -lactam hypersensitivity reactions (see http://depts.washington.edu/druginfo/DTT/2002_Vol31_Files/V31N1.pdf), the most useful tool in evaluating a patient’s potential for a type I, IgE-mediated reaction to penicillin is the allergy history. The accurate interpretation of risk for a true allergic reaction enables the prescriber to properly guide therapeutic decisions.

Key questions:

- 1. At what age did the penicillin reaction occur?** After avoiding penicillins for at least ten years, 9 out of 10 patients who claim to have a penicillin allergy will have a negative skin test and may be able to safely receive a penicillin.
- 2. Do you remember the reaction? If no, who provided you with this information?** Patients with firsthand recall of their allergic reaction are generally able to provide more reliable information to help confirm symptoms associated with an IgE-mediated reaction.
- 3. How did the penicillin reaction present?** Anaphylaxis, urticaria, angioedema, wheezing, and hypotension are concerning symptoms for an IgE-mediated hypersensitivity reaction.
- 4. How long had you been taking penicillin before the reaction occurred?** Allergic reactions occurring >72 hours after administration are generally not IgE-mediated.
- 5. How was the penicillin administered to you?** IgE-mediated reactions are much more likely with parenteral versus oral administration.
- 6. For what reason were you taking the penicillin?** Rashes can occur with some viral and bacterial infections and may not be related to a penicillin allergy.
- 7. Were you taking any other medications that were new to you when the reaction occurred?** Since rashes can occur with a number of medications other than penicillins, another concomitant medication could be the true cause of the allergic reaction.
- 8. Was the penicillin discontinued? If yes, what was the result?** Penicillin-associated maculopapular rashes can spontaneously subside despite continuous therapy with the drug and may not recur upon re-exposure suggesting a non-IgE-mediated allergic reaction.
- 9. Have you taken any other β -lactam antibiotics since the reaction occurred?** If yes, did you have an allergic reaction? Some patients may have been safely treated with another β -lactam antibiotic which would argue against a true IgE-mediated penicillin allergy.

Key points:

- Penicillins should be avoided in patients with a history of an immediate IgE-mediated penicillin allergy.
- It appears that cephalosporins can be safely administered to patients with non-IgE-mediated penicillin allergies.
- Imipenem should not be administered to patients with a positive penicillin skin test or a concerning history of a type I allergic reaction to penicillin.
- Monobactams appear to lack immune cross-reactivity with the penicillins and most authorities consider the use of monobactams safe, even in patients with true penicillin allergies.

Vol. 34, No. 6

Newsletter: Daptomycin: Beyond FDA-Approved Indications, 29-31

Penicillin Allergy: Asking the Important Questions, 32

Supplement: Contemporary Issues in Drug Therapy



DRUG INFORMATION CENTER
Box 354735
Seattle, WA 98195-4735

drug therapy topics