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Review

Daptomycin: The role of high-dose and combination therapy for Gram-positive infections

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ABSTRACT

Daptomycin, a cyclic lipopeptide with rapid bactericidal activity, is approved at doses of 4 mg/kg and 6 mg/kg for the treatment of its respective indications [i.e. complicated skin and soft-tissue infections (cSSTIs) caused by Gram-positive bacteria; and *Staphylococcus aureus* bacteraemia associated with right-sided infective endocarditis (RIE) or cSSTIs, or RIE due to *S. aureus*]. Higher doses and combination therapy strategies have been investigated in some difficult-to-treat infections in order to: enhance clinical success rates; treat pathogens that may be non-susceptible to standard doses; and minimise the risk of resistance development in patients, particularly those who may need an extended treatment duration, who may have had suboptimal surgical management and/or who may have not responded to prior antibiotic therapy. Although clinical trial data of daptomycin doses >6 mg/kg and of daptomycin in combination with other antibiotics are limited, clinical experience reported to date suggests that daptomycin is effective and well tolerated at higher doses and in combination. In this review, the rationale both for high-dose and combination therapy strategies with daptomycin is explored and the available evidence is presented by indication and evaluated from a clinical perspective. Safety and efficacy are discussed from prospective and retrospective clinical studies, together with case reports for a variety of infections, including bacteraemia, endocarditis, cSSTIs and osteomyelitis, and expert recommendations are provided in summary of the evidence. The use of high-dose daptomycin, alone or in combination, may be useful for difficult-to-treat Gram-positive infections and further evaluation of these strategies is warranted.

1. Introduction

Daptomycin (Cubicin®; Novartis Europharm Ltd., Basel, Switzerland) is a broad-spectrum, cyclic lipopeptide antibiotic that is currently approved at a dose of 4 mg/kg daily for the treatment of complicated skin and soft-tissue infections (cSSTIs), at 6 mg/kg daily for right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and for *S. aureus* bacteraemia (SAB) when associated with RIE or cSSTIs [1]. Large pivotal trials with daptomycin have demonstrated that daptomycin monotherapy is non-inferior to standard-of-care agents (including semisynthetic penicillins and vancomycin) for the treatment of cSSTIs and SAB with or without infective endocarditis (IE) [2–4]. However, it is widely felt that the optimal dose for the treatment of certain difficult-to-treat infections has not been defined. Furthermore, there is a paucity of clinical data on the use of daptomycin in combination with other antibiotics, despite frequent use of this treatment strategy in clinical practice. This review explores the rationale for the use of daptomycin both at higher-than-approved doses and in combination, and presents the currently available data for these treatment strategies.

The mode of action of daptomycin involves cell membrane depolarisation with minimal cell lysis [1]. The drug is rapidly bactericidal against Gram-positive organisms, including *S. aureus*, coagulase-negative staphylococci (CoNS) and enterococci [5]. Daptomycin has activity against many drug-resistant pathogens, including meticillin-resistant *S. aureus* (MRSA), heteroresistant vancomycin-intermediate *S. aureus* (hVISA) [6], vancomycin-resistant *S. aureus* [7] and vancomycin-resistant enterococci (VRE) [8]. The pharmacokinetic/pharmacodynamic (PK/PD) predictors of daptomycin efficacy are the ratio of peak exposure [maximum concentration (C_{max})] to the minimum inhibitory concentration (MIC) and the ratio of total exposure [area under the concentration–time curve at 24 h (AUC_{24h})] to MIC (AUC_{24h}:MIC) [9,10]. Daptomycin has linear and concentration-dependent pharmacokinetics with doses up to 12 mg/kg in healthy volunteers (Table 1) [11,12].

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Table 1
Daptomycin[a] pharmacokinetic parameters in healthy volunteers at steady state [11].

Parameter [mean (S.D.)]	Daptomycin dose (mg/kg)			
	6	8	10	12
C_{max} (mg/L)	93.9 (6.0)	123.3 (16.0)	141.1 (24.0)	183.7 (25.0)
C_{min} (mg/L)	6.7 (1.6)	10.3 (5.5)	12.9 (2.9)	13.7 (5.2)
$AUC_{0–24}$ (mg h/L)	632 (78)	858 (213)	1039 (178)	1277 (253)
$t_{1/2}$ (h)	7.9 (1.0)	8.3 (2.2)	7.9 (0.6)	7.7 (1.1)
CL_T (mL/h/kg)	9.1 (1.5)	9.0 (3.0)	8.8 (2.2)	9.0 (2.8)
V (L/kg)	0.101 (0.007)	0.101 (0.013)	0.098 (0.017)	0.097 (0.018)

S.D., standard deviation; C_{max}, maximum concentration; C_{min}, minimum concentration; $AUC_{0–24}$, area under the concentration–time curve from 0 to 24 h; $t_{1/2}$, elimination half-life; CL_T, total plasma clearance; V, volume of distribution.
The rate of free (active) drug is 7–10%.
[a] Administered by 30 min intravenous infusion.

Because the drug is 90–93% reversibly bound to human plasma proteins, it is important to consider the concentration of free drug achieved in tissues in context with the MIC breakpoints for key pathogens (Table 2): at doses at which the minimum concentration (C_{min}) is at or below the breakpoint, there is a risk of resistance developing. Its concentration-dependent activity, linear pharmacokinetics and favourable safety profile are key drivers that support the investigation of high doses of daptomycin.

1.1. Rationale for high daptomycin doses and combination therapy

In difficult-to-treat infections that have a high bacterial burden and sequestered foci of infection (e.g. valve vegetations and abscesses) and for which there is difficulty in achieving adequate local antibiotic concentration at the site of infection or in patients with sepsis and high volumes of distribution and increased renal clearance, the rationale for high-dose daptomycin is two-fold: to increase activity and to prevent resistance. A second approach to achieve these goals is through the use of combination therapy. In enterococci, resistance to daptomycin is conferred by mutations in the genes encoding the LiaF protein (part of the LiaFSR regulatory system) and the GdpD enzyme (involved in phospholipid metabolism), ultimately increasing the positive charge of the cell surface [15]. In staphylococci, mutations identified as conferring resistance include the MprF and Dlt pathways, both resulting in modification of the net surface charge [16]. Antibiotics inhibiting cell wall synthesis, such as β-lactams (and probably fosfomycin), reduce the charge of the outer membrane, thus enhancing binding of daptomycin [17–20]. Enhanced efficacy can be achieved through synergistic combinations: for daptomycin, these include β-lactams (oxacillin, nafcillin and ceftaroline against MRSA [17,18,21] and ampicillin against enterococci [20,22]), fosfomycin [19], gentamicin [23,24] and trimethoprim/sulfamethoxazole (SXT) [25,26].

Table 2
Daptomycin clinical minimum inhibitory concentration (MIC) breakpoints (mg/L).

Organism	EUCAST [13]		CLSI [14]	
	Susceptible	Resistant	Susceptible	Resistant
Staphylococcus spp.	≤1	>1 [a]	≤1	–[b]
Streptococcus spp.				
Groups A, B, C, G	≤1	>1 [a]	≤1	–[b]
Viridans group	–	–	≤1	–[b]
Enterococcus spp.	IE	IE	≤4	–[b]

EUCAST, European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical and Laboratory Standards Institute; IE, insufficient evidence (that the species in question is a good target for therapy with the drug).
[a] Isolates with MICs above the susceptible breakpoint are very rare or not yet reported.
[b] The absence or rare occurrence of resistant strains precludes defining any results categories other than susceptible.

Combination with rifampicin has also demonstrated synergy against staphylococci and enterococci [22,27–29]. In addition, gentamicin (combined with daptomycin) was able to prevent the development of high-level daptomycin resistance (MIC ≥256 mg/L) in >90% of rabbits with *Streptococcus mitis* experimental endocarditis [30].

Literature both for high-dose daptomycin therapy and for combination therapy with daptomycin has previously been reviewed individually. In 2011, Wu et al. published a review evaluating the use of a high-dose treatment strategy for daptomycin (>6 mg/kg) specifically in cSSTIs and bacteraemia [31], and in 2009 Steenbergen et al. reviewed the in vitro and animal model data for combination therapy [32]. This review is the first to address these closely related treatment strategies together, with specific consideration of the potential safety implications and additional evidence of its use in non-approved indications.

2. Bacteraemia

Bacteraemia is a significant cause of mortality among hospitalised patients [33]. Gram-positive bacteria are frequent causes of bacteraemia, with *S. aureus* and CoNS being the most common causative pathogens [33,34]. SAB, in particular, is associated with a high rate of recurrence and mortality as well as a high risk for development of metastatic infections [35]. The risk of clinical failure and resistance development reported in some cases of SAB treated with daptomycin at 6 mg/kg [3,36], while typically associated with inadequate source control such as lack of surgical intervention, might be reduced with higher doses. This is reflected in the Infectious Diseases Society of America (IDSA) guidelines for MRSA infections, which include a recommendation for daptomycin 8–10 mg/kg for complicated bacteraemia, and daptomycin 10 mg/kg in combination with either gentamicin, rifampicin, linezolid, SXT or a β-lactam antibiotic for persistent MRSA bacteraemia and for cases that have not responded to vancomycin treatment [37].

Preliminary results are available from a multicentre, randomised, double-blind trial of 36 patients with MRSA bacteraemia, including RIE treated with daptomycin 10 mg/kg (n = 19) or dose-optimised vancomycin (target trough 15–20 mg/L; n = 17). For the modified intent-to-treat population, clinical cure at the end of therapy was 67% (6/9) for daptomycin and 50% (3/6) for vancomycin. The median time to clearance was 4 days with daptomycin (<50% of vancomycin-treated patients achieved clearance), with a mean length of stay after start of study drug of 7.6 days with daptomycin and 10.8 days with vancomycin [38]. Further comparative data come from a retrospective matched cohort of 170 patients in which high-dose daptomycin was compared with dose-optimised vancomycin (target trough 15–20 mg/L) for the treatment of MRSA bacteraemia with vancomycin MIC >1 mg/L [39]. In the daptomycin group, all patients received <72 h of vancomycin (median 1.7 days) prior to switching to daptomycin. The median dose of