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Daptomycin in paediatrics: current knowledge and the need for future research

Nicola Principi[1], Michela Caironi[1], Francesca Venturini[2], Luca Pani[3] and Susanna Esposito[1]*

[1]*Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [2]*Pharmacy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [3]*Agenzia Italiana del Farmaco, Rome, Italy*

*Corresponding author. Tel: +39-02-55032498; Fax: +39-02-50320206; E-mail: susanna.esposito@unimi.it

To overcome the problems stemming from antimicrobial resistance, there have been several attempts to develop new antimicrobials in recent years. Of the highly potent drugs targeting resistant Gram-positive bacteria, daptomycin has a number of attractive characteristics that suggest its possible use in the treatment of serious infections due to these organisms. Although several pharmacokinetic and clinical studies in adults have provided data to determine how this drug should be prescribed to obtain the maximal clinical efficacy without significant risks of severe adverse events, we have not yet solved all of the problems related to the use of this antibiotic in paediatric patients. In this paper, the resolved and lingering problems of daptomycin treatment in newborns and children are reviewed and discussed. Studies have indicated that daptomycin is a promising therapeutic option for the treatment of paediatric diseases caused by MDR Gram-positive bacilli. However, before daptomycin can be licensed for use in newborns and children, further studies are needed to establish the appropriate dosages for paediatric patients of different ages. The data collected in adults can only be transferred to children older than 12 years, and the information available is not sufficient to determine the dosage that will assure the highest antimicrobial efficacy with only marginal risks of adverse events in younger patients. Thus, studies in neonates and younger infants are urgently needed to permit the use of daptomycin in the first months of life, a period in which infections due to MDR Gram-positive pathogens are increasing.

Keywords: antibiotic resistance, *Enterococcus*, Gram-positive bacteria, *Staphylococcus aureus*, *Streptococcus pneumoniae*

Introduction

MDR bacteria pose a major threat to patients worldwide. Although these organisms remain relatively uncommon overall, their incidence is steadily increasing, with associated increases in mortality and pharmacoeconomic impact.[1] To overcome these problems, there have been several attempts to develop new antimicrobials that are effective against these bacteria in recent years. Of the drugs with high potency against resistant Gram-positive bacteria, daptomycin has a number of attractive characteristics that suggest its possible use in the treatment of serious infections due to these organisms.[2] However, while several pharmacokinetic and clinical studies in adults have provided data regarding how this drug should be prescribed to obtain the maximal clinical efficacy without significant risks of severe adverse events, we have not yet solved all of the problems related to the use of this antibiotic in paediatric patients.[2] Paediatric dosages and the safety and tolerability of the drug, particularly in neonates and young infants, have not been definitively established. This explains why daptomycin is approved by both the FDA[3] in the USA and the EMA[4] in Europe for the treatment of adult patients with complicated skin and soft tissue infections (SSTIs) and *Staphylococcus aureus* bloodstream infections (bacteraemia) associated with right-sided infective endocarditis but is not licensed for use in paediatric patients. However, because of the potential importance of this new drug in the treatment of severe infections due to highly resistant Gram-positive pathogens in the paediatric population, there have been several attempts to better characterize the pharmacokinetics, efficacy, safety and tolerability in children of different ages. In this paper, the resolved and lingering problems related to the possible use of daptomycin in paediatric patients are reviewed and discussed.

Antimicrobial activity of daptomycin and its potential relevance in paediatrics

Daptomycin, a fermentation product derived from *Streptomyces roseosporus*, is a cyclic lipopeptide antibiotic that has at least three very interesting microbiological characteristics: its efficacy against most Gram-positive organisms, including *Staphylococcus* and *Enterococcus* species resistant to vancomycin, linezolid and quinupristin/dalfopristin;[5–10] a very rapid bactericidal activity;[11] and a very low potential for the development of

resistance.[12] Daptomycin causes the bacterial membrane to depolarize by promoting potassium ion efflux and arrests DNA, RNA and protein synthesis, resulting in bacterial cell death. The 90% MIC for specific organisms is 0.5 mg/L daptomycin for >99% of staphylococci and *Streptococcus pneumoniae* and ≤2 mg/L for enterococci. Only 0.4% of staphylococci have an MIC of 2 mg/L.[11] The bactericidal effect of daptomycin is rapid, with 99.9% of bacteria dying in <1 h.[11] The emergence of daptomycin-non-susceptible Gram-positive bacilli is a rare phenomenon that has been reported in <10 cases, in which under-dosing, prolonged treatment and use in situations where penetration of the infection focus was expected to be limited were considered favouring circumstances.[12]

Moreover, daptomycin seems to have immunomodulatory properties, resulting in the suppression of cytokine expression after pathogen-mediated stimulation of the host immune response, particularly when daptomycin is administered in combination with vitamin E.[13] The only limit of daptomycin is its interaction with pulmonary surfactant, which inhibits antibacterial activity and reduces efficacy in the treatment of alveolar pneumonia.[14]

In paediatric patients, infections caused by highly resistant *Staphylococcus* and *Enterococcus* species and *S. pneumoniae* can cause considerable morbidity and mortality. Neonates and children of any age with severe chronic underlying disease, including those with primary or secondary immunodeficiency, are the subjects that more commonly suffer from infections due to these bacteria.[15–17]

S. aureus is responsible for the majority of the most severe bacterial SSTIs[18] and causes a wide spectrum of invasive diseases, including musculoskeletal infections, complicated pneumonia and endocarditis.[19] For many years, MDR *S. aureus* was only detected in hospital patients suffering from severe chronic disease who had previously received several treatments with broad-spectrum antibiotics. The emergence of community-acquired (CA) MRSA has significantly increased the focus on *S. aureus* diseases.[20–27] A recent evaluation of the trends in invasive MRSA infections in US children during the 2005–10 period found that, of the 875 reported cases, 35% were hospital-onset (HO), 23% were healthcare-associated community-onset (HCACO) and 42% were CA.[25] Moreover, while the incidence of HO and HCACO cases did not vary during the study period, the incidence of invasive CA-MRSA infections increased from 1.1 per 100000 in 2005 to 1.7 per 100000 in 2010. In 2010, the incidence of invasive MRSA was higher among infants aged <90 days compared with older subjects (43.9 versus 2.0 per 100000).[25] Interestingly, the paediatric data differed significantly from the data collected in adults, which reported that a noticeable decline in severe HCACO and CA bacterial infections had occurred in recent years. Similar results highlighting the greater and continuously increasing incidence of CA-MRSA infections in children have been reported in several countries, including China.[23–26] A 6 year review of HO- and CA-MRSA infections in Beijing Children's Hospital indicated that invasive MRSA infections rose from 0.89 per 10000 admissions in 2006 to 3.75 per 10000 admissions in 2011, with a notable increase in CA-MRSA cases (from 0 to 2.43 per 10000 admissions) over the same period.[27]

Enterococcus species, although less common than *S. aureus*, are also possible causes of severe infections in children.[28] Enterococci have grown from relative obscurity to become a leading cause of nosocomial infection. This change has partially been attributed to the growth of susceptible host populations, the increased use of intravascular devices, prolonged hospital stays and widespread antibiotic use.[28] Furthermore, the ease with which enterococci acquire resistance coupled with their capacity to survive in the environment render them uniquely suited as nosocomial opportunists and have resulted in the global dissemination of resistant strains. In children, these pathogens can cause neonatal sepsis, urinary tract infections, meningitis and endocarditis, especially in intensive care and haematology/oncology units.[28]

S. pneumoniae remains one of the most important causes of invasive diseases in children. Bacteraemic pneumonia, sepsis, meningitis and osteomyelitis are the most severe diseases caused by this pathogen, which, although more common among immunocompromised patients, are also extremely common in healthy subjects.[29] An increasing incidence of MDR *S. pneumoniae* strains has recently been reported worldwide, with related medical, social and economic impacts.[30]

All of these microbiological data indicate that the use of daptomycin against MDR Gram-positive bacteria could be important in the treatment of paediatric infections, provided that the effective dosages of the drug for different paediatric populations are determined and its safety and tolerability are clearly defined.

Pharmacokinetic profile of daptomycin and choosing the best dosage for paediatric patients

Adult dosage recommendations are derived from pharmacokinetic studies that provide evidence that an intravenous infusion of the drug has linear pharmacokinetics after a single dose or multiple intravenous doses of up to 12 mg/kg.[31–33] In healthy adult subjects, daptomycin has a protein binding of ∼90%, primarily distributes into the extracellular fluid with a steady-state V of 0.101 L/kg, and has a plasma CL of 0.011 L/kg/h. The drug is almost entirely eliminated through the renal system, with 50% of the administered dose excreted within 24 h as intact drug. This pharmacokinetic profile explains why the CL of daptomycin in patients with renal insufficiency is significantly higher than the CL in healthy subjects and why a reduction in dosage is needed to obtain the same drug exposure as measured in healthy subjects.[31–33] Hepatic metabolism appears to be limited, as no metabolism was observed *in vitro* in human liver microsomes and no metabolites have been identified in the plasma or urine of experimental animals receiving daptomycin.[31–33] The $t_{\frac{1}{2}}$ of daptomycin is ∼8 h. Because a single daily intravenous dose of 4 or 6 mg/kg over a 30 min period was followed by a maximum serum concentration (C_{max}) between 50 and 90 mg/L and a mean drug exposure (AUC) between 400 and 600 mg·L/h, it was decided that these dosages could be considered adequate for the treatment of infections due to susceptible pathogens in adults and they were included in the recommendations for the use of the drug, as these values were associated with cure of the disease in clinical practice.[3,4] Higher dosages of daptomycin alone or in combination with other antibiotics were used only to treat pathogens that were not susceptible to standard doses in order to minimize the risk of the development of resistance in patients, particularly those who might need an extended

treatment duration, who might have had suboptimal surgical management and/or who might not have responded to prior antibiotic therapy.[34] This is in agreement with data collected by Canut *et al.*,[35] who estimated the probability of achieving the recommended value of AUC/MIC ratio by Monte Carlo simulation technique and found that standard dose could be ineffective in the cases due to *S. aureus* with MIC >1 mg/L However, when the doses of daptomycin were intravenously infused into paediatric subjects, the C_{max} and AUC previously obtained in adults were only reached in adolescents.[36] The CL and *V* of the drug were significantly higher in children aged <12 years than in adults and adolescents, with the CL and *V* values having an inverse relationship with the age of the child. This was not surprising, as it has been known for more than 40 years that the four most important processes in pharmacokinetics (i.e. absorption, distribution, metabolism and renal excretion) are different in children than in adults, particularly in the first days and months of life, and that at least some aspects of these processes do not take on adult characteristics for several months or years.[37] Although the developmental differences in absorption and metabolism are not relevant for establishing the optimal daptomycin dosage in children due to the fact that this drug is given intravenously and not significantly metabolized, the changes in distribution and elimination that occur at various paediatric ages play important roles in determining the final concentration of this antibiotic in the blood and tissues. In very young infants, the total body water and the extracellular water content are ∼80% and 45% of the body weight, respectively, in comparison to 55%–60% and 20% in adulthood.[38] Moreover, protein binding is reduced in the first period of life because the blood protein concentration and binding capacity are both reduced during this period.[38] This characteristic can be of particular relevance for drugs with high protein binding such as daptomycin, as these variations could lead to a significant enlargement of the free fraction, which possesses the biological activity, possibly resulting in increased antimicrobial efficacy but also an increased risk of dose-related adverse events. However, from a pharmacokinetic standpoint, all of these differences can lead to a larger *V* and, consequently, a lower peak concentration and drug exposure.[39] Finally, it cannot be forgotten that, although nephrogenesis is completed by 34 weeks of gestation, renal function, particularly glomerular filtration rate and tubular secretion, is significantly impaired at birth, reaching adult values only after the first birthday.[40] All of these observations explain why the AUC and C_{max} after a 4 mg/kg intravenous infusion were 215–271 mg·L/h and ∼40 mg/L, respectively, in children 2–11 years old. These values are at least 30% lower than those reported for adults receiving the same daptomycin dosage.[36] This finding led to the conclusion that only a relevant increase in the amount of administered drug could achieve an adequate C_{max} and AUC. Similarly, the administration of 6 mg/kg daptomycin to subjects with a median gestational age at birth and a postnatal age of 32 weeks (range 23–40) revealed that this dosage could not assure adequate pharmacokinetic parameters, as the median AUC, *V*, CL and $t_{\frac{1}{2}}$ of daptomycin 24 h after administration were 262.4 mg·L/h (range 166.7–340.2), 0.21 L/kg (range 0.11–0.34), 0.021 L/kg/h (range 0.016–0.034) and 6.2 h (range 3.7–9.0), respectively.[41] In contrast, Abdel-Rahman *et al.*[42] administered an 8–10 mg/kg dose of daptomycin to children aged 2–6 years and found proportional increases in C_{max} (68.4 and 79.2 mg/L, respectively) and AUC (429.1 and 549 mg·L/h, respectively), successfully reaching values in the range of those reported in adults treated with 4 mg/kg. Moreover, reports of three infants receiving 12 mg/kg/day daptomycin in two divided doses concluded that this dosage was equivalent to adults treated with 4 mg/kg/day.[43,44] Furthermore, Antachopoulos *et al.*[45] reported that the administration of 15 mg/kg daptomycin to 1–2-month-old infants yielded effective peak concentrations. However, particularly for neonates and younger infants, the optimal daptomycin dosage cannot be considered definitively established, and further studies are needed to evaluate the dose of the drug that assures the greatest efficacy without any risk of relevant adverse events in different paediatric populations. This seems particularly important for septic newborns in the first days of life, as the disease can cause modifications in the pharmacokinetic parameters of these patients, requiring relevant dosage adjustment. Moreover, data on posology in children with renal insufficiency, particularly in those in the first months of life who physiologically have a reduced glomerular filtration rate, have to be precisely defined.

Clinical efficacy and safety of daptomycin

Several studies have evaluated daptomycin efficacy in adults with severe SSTIs that are known or suspected to be due to Gram-positive bacteria or in adults with pneumonia, bacteraemia, endocarditis or prosthetic joint infection due to *S. aureus*.[46–48] Daptomycin was found to be effective even in some clinical conditions where comparator antibiotics had failed. Tatarelli *et al.*[46] reported the successful use of both intravenous and intracatheter lock therapy for catheter-related bloodstream infection due to coagulase-negative staphylococci or enterococci in six out of eight patients who were unsuccessfully treated with vancomycin or cefazolin. A recent meta-analysis of daptomycin efficacy and safety based on 13 randomized controlled trials that included ∼2000 adults suffering from SSTI, bacteraemia or pneumonia showed that this antibiotic was as efficacious as comparator regimens, mainly vancomycin, in the intention-to-treat population [relative risk (RR): 0.98; 95% CI: 0.93–1.03] but had a lower efficacy among the clinically evaluable population (RR: 0.96; 95% CI: 0.93–1.00), probably due to the inclusion of a trial that investigated patients with community-acquired pneumonia.[47] On the other hand, data from the study on community-acquired pneumonia revealed that daptomycin was less efficacious than ceftriaxone, especially when the patients who had previously received effective antibacterial therapy were excluded. The removal of this trial from the analysis led to no differences between daptomycin and its comparators (RR: 0.99; 95% CI: 0.95–1.04). However, while there was no significant difference in all-cause mortality between daptomycin and the comparator group in the global population (RR: 1.17; 95% CI: 0.76–1.79), daptomycin did reduce the duration of treatment. In terms of safety, the meta-analysis reported that the incidence of adverse events was similar for daptomycin and its comparators (RR: 0.88; 95% CI: 0.74–1.04), although severe adverse events were more common in the comparator group.[47] However, while daptomycin exhibited a significantly lower incidence of renal impairment, nausea and headache, its use was associated with a higher incidence of creatine phosphokinase (CPK) elevation over 500 U/L. This adverse event was more common with doses ≥6 mg/kg, a trough concentration of 24.3 mg/L or when multiple doses were given on the same day.[47] However, this elevation was always reversible after

discontinuation of the drug. Anaemia, constipation, diarrhoea, vomiting and injection site reactions were also reported. More severe adverse events were rare and included hypersensitivity reactions (drug rash with eosinophilia and systemic symptoms or anaphylaxis), myopathy, peripheral neuropathy, cases of rhabdomyolysis, arrhythmias, tinnitus, vision changes and eosinophilic pneumonia.[46] However, daptomycin appeared safer than vancomycin, even when administered for long periods of time or at high doses.[48]

In contrast to the data available for adults, there have been few randomized comparative double-blind clinical trials to determine the efficacy and safety of daptomycin in children. Most often, information regarding efficacy and safety is derived from studies that evaluated the pharmacokinetic characteristics of the drug in a significantly reduced number of patients with different ages and different treatment regimens.[42,43] Moreover, other publications focus on the administration of daptomycin to a single patient.[36,41,44,45,49–54] However, daptomycin was effective in most of the cases. One of the best examples is a study including children with a median age of 6.5 years who were suffering from persistent staphylococcal bacteraemia that had failed treatment with vancomycin, clindamycin, rifampicin, aminoglycoside or linezolid and were treated with 4 mg/kg/day daptomycin.[49] In this study, the addition of daptomycin resulted in bacteriological cure in six of seven evaluable cases, with bacteraemia resolving within 72 h.

Some randomized clinical randomized trials have been planned to increase our understanding of daptomycin efficacy in paediatric patients, but none has been completed.[55] Unfortunately, some of the trials have been suspended, included one focusing on the treatment of meningitis. In these trials, the dosage of daptomycin will vary according to the age of the children treated. In particular, the doses planned are 7 and 9 mg/kg/day in children aged 12–17 and 7–11 years, respectively, whereas the dose will be increased to 12 mg/kg/day in children aged 2–6 years. Three of the studies are ongoing with the aim of evaluating daptomycin efficacy.[55] Study DAP-PEDS-07-03 is enrolling subjects with SSTIs caused by Gram-positive pathogens. Approximately 396 children are being randomized, stratified by age group, to receive either daptomycin or standard care in a 2:1 ratio, with a target of ∼264 children receiving daptomycin. Enrolment has been completed in thee age groups (12–17, 7–11 and 2–6 year olds), and is ongoing for the 12–24 month age group. Study DAP-PEDS-11-02 is focused on subjects with *S. aureus* bacteraemia. Approximately 75 children will be randomized, stratified by age group, to receive either daptomycin or standard care in a 2:1 ratio. DAP-PEDOST-11-03 is a multicentre, randomized, double-blind comparative study that will evaluate daptomycin versus an active comparator in paediatric subjects with acute haematogenous osteomyelitis due to Gram-positive organisms.[55] At the moment, there are no ongoing randomized controlled trials in neonates and in children with renal insufficiency.

The safety and tolerability data from the various studies cannot be pooled because different posologies have been prescribed in most of the cases. Moreover, the total number of children treated with daptomycin is very low, as no more than a few hundred paediatric patients have received this antibiotic globally. However, a global evaluation of the tolerability and safety of daptomycin in children does not seem to differ substantially from the safety and tolerability found in adults.[43–54] Even high dosages were not associated with a significant number of adverse events, which were always mild and reversible. Only phlebitis, infusion site reactions and headache were attributed to daptomycin, and all of these adverse events resolved without intervention. No severe adverse events were reported and no interruption of therapy was needed. Interestingly, increases in CPK or muscular problems were not reported. Despite these apparently favourable results, definitive conclusions about the tolerability and safety of daptomycin in children cannot be drawn, and additional data from larger study samples are needed. Once again, this seems particularly important for children such as neonates and younger infants, who must be treated with the highest dosages, sometimes twice per day. This precaution is necessary because CPK elevation and drug-induced myopathy appear to increase not only with the dosage but also with the frequency of dosing.[47]

Conclusions

Daptomycin is a promising therapeutic option for the treatment of paediatric diseases due to MDR Gram-positive bacilli. These pathogens are increasingly common among children, particularly in the first days and months of life, and in children with a chronic underlying disease. Daptomycin has microbiological characteristics that suggest that the data collected *in vitro* might be confirmed by intravenous administration *in vivo*. However, further studies aimed at establishing the adequate dosage for different paediatric ages are needed before daptomycin can be licensed for use in newborns and children. The data collected in adults can only be transferred to children older than 12 years. For younger patients, the information available does not seem adequate to define the dosage that will assure the highest antimicrobial efficacy and only a marginal risk of adverse events. Some studies specifically planned to solve these problems are ongoing in toddlers and school-age subjects. In contrast, no adequate studies of the pharmacokinetics, tolerability and safety of daptomycin are planned in neonates and younger infants. These studies are urgently needed to permit the use of daptomycin in the first months of life, a period in which infections due to MDR Gram-positive pathogens are increasing.

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