Clinical experience with daptomycin: bacteraemia and endocarditis

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Serious infections due to Staphylococcus aureus, especially those due to methicillin-resistant S. aureus, have become a major challenge. Vancomycin has long been the drug of choice for treatment of such infections, but failures due to its slow bactericidal activity coupled with increasing MICs have necessitated a search for new, more effective agents. Daptomycin has been studied by a number of investigators and has proved to be effective for bacteraemic infections due to staphylococci as well as vancomycin-resistant enterococci and other Gram-positive organisms. In addition, in a randomized controlled trial comparing daptomycin monotherapy with potentially synergistic therapy with either vancomycin or β-lactam, both used in combination with an aminoglycoside, daptomycin achieved comparable outcomes but with significantly less nephrotoxicity.

Keywords: MRSA, Staphylococcus aureus, S. aureus

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) was initially observed in the 1960s, but became a widespread clinical problem in the early 1980s. At that time, the only antibiotic considered to have predictable activity against MRSA was vancomycin. Although approved for use in 1958, the drug was largely unused for decades due to its perceived toxicity. With the growing prevalence of serious disease due to MRSA, vancomycin quickly gained favour as the drug of choice to treat these infections. However, it soon became apparent that vancomycin is inferior to β-lactam antibiotics. Levine et al.1 compared vancomycin monotherapy with the combination of vancomycin plus rifampicin in patients with MRSA endocarditis and found not only that monotherapy cleared the bacteraemia on average 2 days faster than the combination but that either approach was associated with prolonged bacteraemia when compared with the known results of treatment with nafcillin or nafcillin plus aminoglycoside. In a study of patients with methicillin-susceptible S. aureus (MSSA) infection, Small and Chambers2 also reported disappointing results when using vancomycin and attributed the results to the delayed bactericidal activity of vancomycin. Recently, S. aureus became the leading cause of nosocomial bacteraemia and supplanted viridans group streptococci as the leading worldwide cause of infective endocarditis,3 and a newly recognized type of community-associated MRSA began to cause infection throughout the world.4 In addition, infections due to vancomycin-resistant enterococci (VRE) became a problem, and S. aureus with reduced susceptibility to vancomycin were discovered, first in Japan and subsequently throughout the world.5

To add to growing concerns about the utility of vancomycin, it is now recognized that there has been an increase in the MICs of vancomycin for MRSA, leading to a reduction in the breakpoint between susceptible and resistant strains from 4 to 2 mg/L. Even for MRSA with vancomycin MICs within the susceptible range, there has been a steady upward trend towards higher MICs over time.6 The clinical significance of these findings is becoming clear as recent reports document therapeutic failures even when isolates are within the susceptible range.7 All of this has led to the search for alternatives to vancomycin.

Pre-clinical studies

Daptomycin has been studied extensively in vitro as well as in vivo. Rouse et al.7 assessed the in vitro activity of various antibiotics against MRSA isolated from patients with endocarditis and found daptomycin to be bactericidal against all isolates. Piper et al.8 also tested the in vitro activity of daptomycin against a number of viridans group streptococci isolated from patients with endocarditis as well as several other Gram-positive organisms that are unusual causes of endocarditis. The daptomycin MIC90 ranged from ≤0.125 to 0.5 mg/L for MRSA, viridans group streptococci and penicillin-resistant Streptococcus pneumoniae and was 4.0 mg/L for Enterococcus spp. The MIC range for the ‘unusual’ isolates was ≤0.125–2.0 mg/L. In an endocarditis model using simulated vegetations, daptomycin eradicated MRSA much faster than a synergistic combination of vancomycin plus an aminoglycoside.9 In that study, when daptomycin was combined with a single dose of gentamicin, the
combination reduced bacteria to the level of detection faster than daptomycin monotherapy, but the two regimens were equivalent by 48 h. Daptomycin also proved to be effective in an animal model of MRSA endocarditis, and the results were improved by the addition of rifampicin. In another study comparing the ability of various antibiotics to eradic ate staphylococci embedded in biofilm, as would be encountered in patients with prosthetic valves or infected catheters, daptomycin proved to be most effective after short-term exposures simulating antibiotic lock therapy. In another study assessing the ability of antibiotics to eradicate vancomycin-resistant Enterococcus faecium from biofilm, daptomycin and minocycline were the most active and led to a significant reduction in growth; however, the activity of daptomycin was superior to minocycline (P < 0.001). In contrast, in a different study, vancomycin and linezolid both failed to eradicate staphylococci and enterococci from biofilm. Also, of particular importance in the treatment of patients with infective endocarditis, in earlier studies, daptomycin was shown to penetrate homogeneously into the core of cardiac vegetations. In contrast, vancomycin remained confined to the periphery of vegetations, only slowly coming into contact with organisms deep within the core. These and similar data have encouraged a number of investigators to study daptomycin in both observational and controlled studies in patients with either bacteraemia or infective endocarditis.

Clinical studies

Most reports of daptomycin use for the treatment of endocarditis or bacteraemia are from observational series or case reports. In a retrospective analysis, Segre ti et al. described 31 patients who received daptomycin, either 4 or 6 mg/kg, for the treatment of infective endocarditis or bacteraemia. Most patients had failed previous therapy with other agents, were intolerant or allergic to other antibiotics or were infected with VRE. In this study, failure was defined as persistence of signs and symptoms of infection, persistently positive blood cultures while receiving daptomycin or death. Overall, 30 patients were bacteraemic and 9 had infective endocarditis (1 had culture-negative endocarditis). The most common pathogens were MRSA and VRE (11 patients each). Seven patients were infected with MSSA and one was infected with coagulase-negative staphylococci (CoNS). Previous therapy consisted of vancomycin in 18 patients, linezolid in 4 patients and oxacillin in 3 patients. Overall, 24 of the 31 patients who were treated with daptomycin improved or were cured, whereas 7 patients died while in hospital. Infection was cured in all 11 patients who were treated for MRSA, in 6 of the 7 (86%) with MSSA and in 5 of the 11 (45%) infected with VRE. Among endocarditis patients, daptomycin therapy was successful in six of nine (67%). Daptomycin therapy was successful in 16 of the 20 (80%) bacteraemic patients who did not have endocarditis and in six of the nine (67%) who had endocarditis. VRE was the infecting pathogen in six of the seven who died. The seventh was switched to oxacillin when MSSA infection was diagnosed, but died. She received only 4 days of treatment with daptomycin. One patient was readmitted with infection due to a different organism. In a different report, daptomycin monotherapy failed to eradicate VRE infection but resulted in cure when gentamicin and ampicillin were added to the regimen. In another case report, a haemodialysis-dependent patient with Corynebacterium striatum endocarditis remained bacteraemic after receiving linezolid for 1 week. Treatment was changed to daptomycin 6 mg/kg every 48 h to accommodate her renal failure and rifampicin twice daily was added. She defervesced within 24 h and blood cultures were negative within 4 days. At a 3 month follow-up, there was no evidence of endocarditis.

Poutsia ka et al. reported the results of daptomycin treatment in nine neutropenic patients who had VRE infection with bacteremia, all but one of which were due to E. faecium. Two patients received daptomycin at only 4 mg/kg, while the remainder were treated with 6 mg/kg. Four of the nine patients were cured; two died 3 days after starting treatment. Four patients had dosage reductions due to renal failure, of which three died. The authors commented that the overall results might have been improved had patients been treated with higher doses of daptomycin. Two neutropenic bone marrow transplant patients who failed vancomycin therapy for line-related Leuconostoc infections were successfully treated with line removal and daptomycin at 6 mg/kg.

Several authors have reported the results of daptomycin therapy in patients with prosthetic valves or other implanted devices. One such report describes a patient who refused surgical therapy for prosthetic valve endocarditis and paravalvular abscess due to MRSA. The patient received vancomycin for 9 days followed by linezolid for 2 days before being switched to daptomycin (6 mg/kg) because of sustained bacteraemia. Blood cultures became negative 5 days after starting daptomycin. Treatment was subsequently changed to oral linezolid to complete the course of therapy and the patient survived. In another report, a patient who had persistent MSSA bacteraemia from an infected automatic implanted cardiac defibrillator and an infected coronary stent received daptomycin at 6 mg/kg for 9 days followed by high dose (12 mg/kg) for an additional 41 days with resolution of the infection and without evidence of toxicity. The patient was also treated with concomitant linezolid for 10 days and gentamicin for 9 days. Daptomycin was also used successfully in a patient who had an infected intra-aortic counter pulsation device with associated persistent MRSA bacteraemia. Despite therapy first with linezolid and then linezolid combined with rifampicin, the patient remained bacteraemic. Therapy was switched to daptomycin 6 mg/kg as a loading dose followed by 4 mg/kg thereafter. Blood cultures cleared after 3 days after which the patient underwent cardiac transplantation. Multiple intraoperative cultures obtained from the assist device were negative.

Two large studies evaluated patients treated for bacteraemia or endocarditis in a registry. The data in this registry, the Cubicin Outcomes Registry and Experience 2004 database, allow retrospective analysis of patients in order to obtain information about real-world clinical experience with daptomycin. Sakoulas et al. described the results of treatment in 126 patients with bacteraemia, 86% of whom received daptomycin after previous antibiotic therapy. MRSA, VRE and CoNS were the most common organisms treated. The median duration of therapy was 12.5 days and 69% received at least one dose of a concurrent antibiotic, usually a cephalosporin, fluoroquinolone or metronidazole. Success ranged from 88% for MRSA to 100% for MSSA. The success rate for daptomycin monotherapy was 92% compared with 87% for those who received daptomycin in combination with another antibiotic. The overall clinical success rate for daptomycin was 89% and was independent of baseline renal function, daptomycin dose, pathogen, first-line use or concomitant antibiotic therapy. In a similar analysis of patients in...
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the registry who were treated for endocarditis, Levine and Lamp25 reported the results of 49 patients who received daptomycin. In this study, 38 patients had left-sided or both left-sided and right-sided endocarditis and 11 had right-sided infection alone. Renal failure was common in this population, 29% of whom were receiving haemodialysis. MRSA and VRE were the most common pathogens and, as was found in the study of Sakoulas et al.,24 88% received prior antibiotic therapy. The median starting dose of daptomycin was 6 mg/kg, but 55% ultimately received a dose of >6 mg/kg. Daptomycin therapy was successful in 63%; cure was seen in 37% and improvement in 26%. Therapy failed in 8%; 29% were unevaluable. There were no differences in clinical response based on baseline renal function, primary pathogen or site of endocarditis. As with the study of Sakoulas et al.,24 many patients had concomitant therapy with other antibiotics, making the outcome in some cases difficult to interpret. Other limitations of the study are the uncontrolled nature of the observations, including the veracity of the diagnosis and the retrospective analysis. Thus, the results from a randomized, controlled study of patients with bacteremia or endocarditis are critical. Other reports and literature are extensively reviewed elsewhere in this Supplement in the paper by Warren.26

Fowler et al.27 conducted a randomized comparison of daptomycin versus standard therapy consisting of either vancomycin or β-lactam plus an aminoglycoside given for the first 4 days of therapy. It is noteworthy that this was the first randomized comparative trial for treatment of endocarditis since the comparison between β-lactam monotherapy versus combination of β-lactam and aminoglycoside published in 1982.28 In that study, the patients in the combination arm received the aminoglycoside during the first 2 weeks of the treatment course. Although bacteremia cleared faster in the patients on combination therapy, the eventual outcome was the same for both groups, although there was more renal failure in patients receiving the aminoglycoside. Thus, in the daptomycin study, gentamicin was given for only 4 days in an attempt to achieve the early benefit of synergistic treatment while avoiding the eventual toxicity associate with prolonged aminoglycoside use. Prior to entering the study, patients had to have a positive blood culture for Staphylococcus aureus. Within 5 days of study entry, patients had a transesophageal echocardiogram and were categorized as having either complicated or uncomplicated bacteremia or endocarditis based on the Duke criteria. The primary endpoint of the study was the outcome at a 6 week test-of-cure visit, during which blood cultures were required to verify clearance of the bacteremia. A secondary endpoint was the clinical status and blood culture result at the end of the treatment period. As this was an open-label study, a blinded adjudication committee composed of experts in the field of infectious disease and endocarditis evaluated the case notes of each patient to confirm the diagnosis and the outcome. It is important to note two additional features of this trial that had an impact on the outcome. First, as noted above, this was a study comparing daptomycin monotherapy with potentially synergistic combination therapy. In addition, as a non-inferiority study, by its very design, the results were not anticipated to demonstrate clear advantage of either therapeutic regimen. Patients with left-sided endocarditis were excluded from the study until the trial was nearly completed; hence, very few patients with mitral or aortic valve disease were enrolled.

In both arms of the study, patients with left-sided infection failed therapy. However, it appears that the reason was failure to provide drainage or valve replacement surgery when indicated. With the exception of those with left-sided endocarditis, the study verified that daptomycin was equivalent to the synergistic combinations for both MSSA and MRSA bacteremia and right-sided endocarditis. Among patients treated with daptomycin, the success rate at the 6 week test-of-cure visit was 54.4% compared with 55.3% in the control population. However, differences among patients treated for MRSA infection were more apparent. Patients with uncomplicated bacteremia in both groups had the highest success rates (56.3% and 55.2% for the daptomycin and control groups, respectively). There was a greater difference (again not significant) in patients with complicated bacteremia (43.3% versus 37.7% for daptomycin and control groups). The greatest differences occurred in patients with right-sided endocarditis. The success rate in those with uncomplicated right-sided MRSA endocarditis treated with daptomycin was 50% versus 25% in the comparator arm. Success rates favoured the comparator in those with complicated right-sided endocarditis (50% versus 38.5% for comparator versus daptomycin, respectively). In the entire population treated for MRSA bacteremia, the success rate was higher for daptomycin-treated patients (44.4% versus 31.8% for daptomycin and controls, respectively). It is important to note that the clinical outcome for patients in both arms of the study was higher than the reported final results. As it was a registration study, many patients were labelled as failures for administrative reasons (e.g., failure to obtain blood culture at test-of-cure visit). In fact, the clinical success rate in both arms was ~70%. It is also noteworthy that the results for MSSA infection were almost identical for either treatment arm (48.6% and 44.6% for comparator versus daptomycin, respectively). In view of the previous failures of vancomycin in patients with MSSA infection,2 the equivalent results of daptomycin and β-lactam therapy in this study suggest that daptomycin might prove to be effective empirical treatment pending susceptibility information. Adverse events were similar in both groups except for changes in renal function. Despite limiting aminoglycoside use to only 4 days, patients receiving both comparator regimens containing aminoglycoside were significantly more likely to have decreases in renal function (26.3% versus 11.0% for comparator versus daptomycin, P = 0.004).

In the above bacteremia trial, MICs of both daptomycin and vancomycin increased for bacterial isolates from a few patients. These increased MICs were associated with failures of therapy, but these failures were seen in patients who did not receive customary surgical drainage or removal of infected devices. However, there are increasing reports describing therapeutic failure due to increases in daptomycin MIC, most often in patients initially treated with vancomycin.29–33 An association between vancomycin and daptomycin heteroresistance was found in vitro by Sakoulas et al.,34 and in one case with a very well-characterized MRSA, the organism was noted to develop sequential changes in the cell wall that ultimately led to an elevated daptomycin MIC.35 In another study using simulated vegetations, changes in MIC were prevented by increasing the simulated dosage of daptomycin to 10 mg/kg.36 Increasing the dose from the approved 6 mg/kg to a higher dose may prove to prevent such changes, but studies to assess this approach are ongoing and no recommendation can be made at present.

In conclusion, daptomycin has been used very successfully to treat S. aureus and enterococcal infections and is a welcome addition to our therapeutic armamentarium. In an era when
MRSA are prevalent and empirical therapy is frequently required prior to identifying the infecting pathogen, it is encouraging that daptomycin has been demonstrated to be effective against both MRSA and MSSA in patients with serious bacteraemic infections. Future studies will undoubtedly provide useful information regarding the dose that will afford the greatest efficacy with the least concern for the development of resistance.

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