Daptomycin in synovial fluid during treatment of methicillin-resistant Staphylococcus aureus septic arthritis

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Sir,

Methicillin-resistant Staphylococcus aureus (MRSA) osteoarticular infections present a therapeutic challenge, requiring the adequate removal of infected materials and antibiotic penetration to give therapeutic concentrations at the infection site. Daptomycin, a cyclic lipopeptide antibiotic with a broad spectrum of activity against Gram-positive organisms including MRSA, is an emerging therapy in osteoarticular infection. However, to our knowledge, there are no data on daptomycin osteoarticular tissue penetration. Herein, we report therapeutic intra-articular concentrations in a case of daptomycin-treated MRSA septic arthritis.

A 41-year-old man with haemoglobin S/C disease (a sickle-cell disorder) and asymptomatic, antiretroviral-therapy-naive HIV infection presented with a hot, swollen left knee. A long complicated history of recurrent MRSA infection involving his left hip, femur and knee followed an infected total hip replacement 6 years previously. Despite a Girdlestone procedure, extensive chronic osteomyelitis had developed. Prolonged suppressive antibiotic therapy was associated with a 3 year period free of overt infection. Knee aspiration revealed thick pus and MRSA susceptible to vancomycin, teicoplanin, sodium fusidate, tetracyclines, linezolid and daptomycin, but resistant to rifampicin, trimethoprim and clindamycin. The MIC of daptomycin was 0.38 mg/L by Etest. Antibiotic options were limited by previous hepatotoxicity with glycopeptides and peripheral neuropathy with linezolid. Arthroscopic washout of the joint was performed and 6 mg/kg daptomycin was used in combination with 500 mg of oral sodium fusidate 8 hourly. On day 14 of daptomycin therapy, the left knee was aspirated and samples were collected for culture and daptomycin concentration quantification.

A simultaneously drawn serum sample was also obtained for daptomycin concentration. Synovial fluid was serosanguineous, not blood stained and culture was negative. Samples for daptomycin assay collected in glass and plastic containers were assayed for the presence of daptomycin, as previously described.1 Daptomycin serum concentration was 12.9 mg/L and synovial fluid concentrations were 9.0 mg/L (glass) and 7.3 mg/L (plastic), suggesting that some daptomycin might have bound to the plastic tube (CLSI susceptibility breakpoint for daptomycin MIC of 1 mg/L). Daptomycin was continued with oral sodium fusidate, with clinical response, and therapy was completed via the outpatient parenteral antibiotic therapy service.

Although unlicensed for osteoarticular infections, daptomycin is increasingly used for this indication, often in combination with other agents. Published case reports, mainly where daptomycin is used second line, suggest cure or improvement in 91% of cases.2 However, judging response to therapy retrospectively is difficult in bone and joint infection, particularly as long-term outcome data are so important. In the only randomized, controlled trial data to date, a subgroup with bone and joint infections was identified in a study of complicated S. aureus bacteremia.3 Outcomes in this small group of patients were similar between daptomycin monotherapy and standard therapy, with a successful outcome reported in 67% of patients treated with daptomycin compared with 55% of those treated with standard therapy.

To our knowledge, this is the first time that daptomycin concentrations in synovial fluid have been documented. From preclinical data, it is known that daptomycin penetrates well into skin, both in healthy volunteers and in diabetic patients,4 while it is also found in satisfactory concentrations in experimentally...
induced inflammatory blisters.5 Our finding of synovial fluid daptomycin levels of 70% of serum is similar. In this case, however, daptomycin was assayed opportunistically, as the patient required repeat knee aspiration for culture after 2 weeks of therapy. It is probable, therefore, that the concentration of daptomycin in synovial fluid reflects either steady-state concentration or accumulation at the site of infection. The therapeutic daptomycin concentration at the site of infection in synovial fluid associated with clinical improvement when used in combination with sodium fusidate add to the data of daptomycin’s utility in osteoarticular infection. The efficacy of daptomycin in osteoarticular infections should be addressed prospectively in sufficiently powered, randomized, controlled trials.

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Transparency declarations
N. D. R.: none to declare. A. M. L. is a member of the Novartis daptomycin advisory board, UK. R. A. S. is a member of the Novartis daptomycin advisory board, UK and has spoken at Novartis sponsored symposia.

References

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Successful treatment of methicillin-resistant Staphylococcus aureus endocarditis with telavancin

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Sir,
Within our institution, we have recently seen an increase in bloodstream infections due to methicillin-resistant Staphylococcus aureus (MRSA) having decreased responsiveness to glycopeptides. Testing has revealed that these isolates are neither vancomycin intermediate nor heterogeneous vancomycin intermediate. Patients continue to be bacteraemic despite therapeutic levels of vancomycin. In September 2009, the FDA approved telavancin for the treatment of complicated skin and soft-tissue infections. To date, there have been no reports of the use of telavancin in bacteraemic patients. Here we report the successful use of telavancin for MRSA bacteraemia and right-sided endocarditis.

A patient with a history of hepatitis C and intravenous drug use presented with fevers and chills. Blood cultures grew MRSA (vancomycin MIC < 0.5 mg/L, daptomycin MIC < 1 mg/L) and he was begun on 15 mg/kg vancomycin every 12 h. He was found to have septic pulmonary emboli and a pleural effusion. A transoesophageal echocardiogram showed severe tricuspid valve regurgitation with a large tricuspid valve vegetation. Blood cultures remained positive through 8 days of vancomycin treatment with documented trough levels of 15–20 mg/L. Treatment was changed to 10 mg/kg telavancin intravenously every 24 h. Blood cultures became negative within 1 day of the start of telavancin. The patient’s creatinine was monitored and remained stable from admission. The patient underwent a tricuspid valve repair for severe tricuspid regurgitation ~1 month after his initial positive culture. He completed 4 weeks of telavancin and was discharged home in a stable condition 6 weeks after his admission. At follow-up 6 weeks after completing treatment, the patient was afebrile with documented negative blood cultures.

To our knowledge, this is the first case of persistent MRSA bacteraemia treated successfully with telavancin. Telavancin is a lipoglycopeptide with a mechanism of action similar to that of the glycopeptides but with an added mechanism that interferes with cell membrane function.1 It is reportedly rapidly bactericidal against S. aureus,2,3 thus having potential for use in bacteraemic patients. The study of telavancin in MRSA bacteraemia has been completed in murine models with the comparator being vancomycin.4 In this model, telavancin demonstrated greater killing activity than vancomycin, and a statistically significant difference in survival was found between the two groups with 0% survival for vancomycin and 93% for telavancin. These results have been attributed to the dual mechanism of action of telavancin as well as a longer post-antibiotic effect. With the increasing frequency of persistent MRSA bacteraemia with decreased responsiveness to vancomycin and failures reported with daptomycin after vancomycin use,5,6 new therapeutic options are desirable. Clinical studies will be necessary to determine whether telavancin offers advantages over other currently available antibiotics.

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